UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY and MANULIFE INSURANCE COMPANY, Plaintiffs, v. ABBOTT LABORATORIES, Defendant.	CIVIL ACTION NO. 05-11150-DPW

ABBOTT'S DEPOSITION DESIGNATIONS AND COUNTER DESIGNATIONS FOR PERRY NISEN

Defendant Abbott Laboratories ("Abbott") respectfully submits the attached deposition designations and counter-designations for the February 16, 2007 deposition of Perry Nisen, former Divisional Vice-President, Oncology Development (ABT-518)

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Dated: February 18, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By: __/s/ Eric J. Lorenzini_____
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CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 18, 2008.

Date: February 18, 2008.

/s/ Ozge Guzelsu

Perry Nisen Deposition Designations

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
11/22/2006	Nisen, Perry			9:12 - 9:16			
11/22/2006	Nisen, Perry			12:15 - 13:12			
11/22/2006	Nisen, Perry			16:5 - 18:7			
11/22/2006	Nisen, Perry			18:10 - 19:12			
11/22/2006	Nisen, Perry			19:16 - 19:19			
11/22/2006	Nisen, Perry			20:18 - 22:5			
11/22/2006	Nisen, Perry			22:11 - 23:2			
11/22/2006	Nisen, Perry			27:17 - 27:22			
11/22/2006	Nisen, Perry			30:7 - 30:23			
11/22/2006	Nisen, Perry			32:1 - 32:4			
11/22/2006	Nisen, Perry			37:8 - 39:19			
11/22/2006	Nisen, Perry			39:23 - 40:22			
11/22/2006	Nisen, Perry			41:20 - 42:7			
11/22/2006	Nisen, Perry			50:1 - 50:4	Nisen 2		
11/22/2006	Nisen, Perry			51:20 - 52:14			
11/22/2006	Nisen, Perry			57:24 - 62:19			
11/22/2006	Nisen, Perry			63:19 - 65:5			

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
11/22/2006	Nisen, Perry			67:19 - 69:23			
11/22/2006	Nisen, Perry			93:17 - 94:10			
11/22/2006	Nisen, Perry			97:2 - 97:14			
11/22/2006	Nisen, Perry			101:4 - 103:1			
11/22/2006	Nisen, Perry			110:18 - 113:2	Nisen 5		
11/22/2006	Nisen, Perry			114:5 - 117:3			
11/22/2006	Nisen, Perry			119:2 - 120:1			
11/22/2006	Nisen, Perry			138:4 - 138:14			
11/22/2006	Nisen, Perry			149:21 - 150:1	Nisen 10		
11/22/2006	Nisen, Perry			165:20 - 166:17			
11/22/2006	Nisen, Perry			184:8 - 184:15			
11/22/2006	Nisen, Perry			185:6 - 185:11			
11/22/2006	Nisen, Perry			190:18 - 191:12	Nisen 11		
11/22/2006	Nisen, Perry			217:1- 218:14			
11/22/2006	Nisen, Perry			219:2 - 219:11			
11/22/2006	Nisen, Perry			244:16 - 247:6			
11/22/2006	Nisen, Perry			319:2- 320:11			
11/22/2006	Nisen, Perry			337:2-337:5	Nisen 31		

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
11/22/2006	Nisen, Perry			337:22-340:22	31		
11/22/2006	Nisen, Perry			341:1-344:18	32		
11/22/2006	Nisen, Perry			360:7-361:10			
11/22/2006	Nisen, Perry			372:21-373:18	37		
11/22/2006	Nisen, Perry			386:6-387:16			
11/22/2006	Nisen, Perry			389:14-391:9	10		
11/22/2006	Nisen, Perry			391:10-396:5	38		
11/22/2006	Nisen, Perry			396:8-397:16	39		
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Color Key to Deposition Designations

Designation by Plaintiffs

Counter Designation by Defendants

Designation by Defendants

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS
- - -

JOHN HANCOCK LIFE INSURANCE COMPANY, : CIVIL ACTION
JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY, :
and MANULIFE INSURANCE COMPANY (f/k/a INVESTORS PARTNER INSURANCE COMPANY), :
Plaintiffs, :
V. :
ABBOTT LABORATORIES, :
Defendant. : NO. 05-11150-DPW

- - -

November 22, 2006

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CONFIDENTIAL

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Videotaped deposition of PERRY NISEN, M.D., Ph.D., held in the offices of Morgan Lewis, LLP, 18th Floor, 1701 Market Street, Philadelphia, Pennsylvania 19103, commencing at 9:05 a.m., on the above date, before Denise D. Bach, a Federally Approved Registered Professional Reporter and a Certified Shorthand Reporter.

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JASON HOFFMAN, Videographer

will be noted on the stenographic record. The court reporter will now swear in the witness.

- - -

PERRY NISEN, M.D., Ph.D., having been first duly sworn, was examined and testified as follows:

- - -

EXAMINATION

- - -

BY MR. DAVIS:

Q. Good morning. Would you state your name for the record, please?

A. Perry Nisen.

Q. You're a doctor?

A. Yes.

Q. Dr. Nisen, my name is Brian Davis. I represent John Hancock and the other plaintiffs in this action in federal court in Boston. I'm going to be asking you a series of questions here today.

You understand that you're under oath?

again, we'll try to accommodate you as soon as possible thereafter.

Dr. Nisen, where do you live?

A. I live in Wynnewood, Pennsylvania.

Q. What is the street address?

A. 611 Argyle Circle, Wynnewood. That's venue 19096.

Q. How long have you lived there?

A. I've lived there for 14 months.

Q. Where do you work?

A. I work at GlaxoSmithKline.

Q. What position do you hold at Glaxo?

A. I'm senior vice president, clinical pharmacology and discovery medicine.

Q. I'm sorry, would you repeat your title?

A. Senior vice president, clinical pharmacology and discovery

medicine.

Q. You previously worked at Abbott Laboratories?

A. Correct.

Q. When did you leave Abbott?

A. I left there in -- two years ago July. So about 25 months.

Q. So you left in July of 2004?

A. 2000 -- yes.

Q. It was two years ago this past July?

A. Correct. June, July.

Q. Why did you leave Abbott?

A. I had a new opportunity at GlaxoSmithKline.

Q. When did you start with GlaxoSmithKline?

A. A few weeks after leaving Abbott.

Q. Have you held any other positions at GlaxoSmithKline other than your current position?

A. No.

Q. Briefly, what are your

resolved?

A. I was dropped from the complaint. I don't know the legal term for that, though.

Q. Would you give me a brief description of your educational background, please?

A. I have a Bachelor's degree from Stanford, a Master's medical -- M.D. degree and Ph.D. degree from Albert Einstein College of Medicine. I have residency training in pediatrics and subspecialty training in pediatric hematology/oncology. My Ph.D. is in molecular biology.

I'm board certified in pediatrics, pediatric hematology/oncology, although I haven't renewed those boards. And I was a medical school professor and had -- was a full professor and had endowed chair at University of Texas Southwestern Medical School before joining Abbott.

Q. When did you obtain your BA?

A. My?
Q. Your Bachelor's.
A. My Bachelor's, in 1976, '77.
Q. I'm sorry, was that a B -- a Bachelor of Science or Bachelor --
A. Yes, Bachelor of Science.
Q. And you -- where did -- when did you obtain your M.D.?
A. Five years later at Albert Einstein College of Medicine in New York.
Q. So approximately '82?
A. Yes.
Q. And then you obtained a Ph.D. at some later point in time. When did you obtain your Ph.D.?
A. I obtained both degrees at the same time from the same school. It was a combined M.D./Ph.D. program.
Q. And for some period of time, you practiced medicine?
A. Yes.
Q. When?
A. I practiced medicine through residency and as a faculty member until I

left UT Southwestern -- I'm going to have trouble. I -- I don't have my CV in front of me, but I practiced for approximately -- I was on faculty for about -- I guess at least ten years. And I maintained and still maintain a medical license.

Q. Which state?

A. Currently in Pennsylvania.

Q. When you practiced medicine, where did you practice?

A. I practiced in New York for a period of time at Schneider Children's Hospital and Columbia-Presbyterian Medical Center, and then I practiced at University of Texas Southwestern Medical Center in Dallas.

Q. You said you -- you actually were a medical school professor --

A. Correct.

Q. -- at the University of Texas?

A. Correct.

Q. Teaching what?

A. In the department of pediatrics, clinically, and genetics and development in the basic sciences.

Q. You left that position to join Abbott Laboratories?

A. Correct.

Q. What year was that? As best you recall.

A. I've been at GSK for two years, and I was at Abbott for eight years. So over ten years ago. Around ten years ago.

Q. So approximately 1996?

A. Yeah, '96, '97, I think is the year.

Q. What position did you first hold when you joined Abbott?

A. Divisional vice president, cancer research.

Q. How did it come about that you went to work for Abbott at that point in time?

A. I was invited to give a lecture there, and after that lecture

there -- I had a colleague there that I worked with at Stanford many years ago. He invited me to give a lecture. After my lecture, they recruited me to this position. And I accepted it.

Q. When you took the position as divisional vice president of cancer research, was that -- were you required to move to the Chicago area?

A. Yes.

Q. All the time that you worked at Abbott, did you work in the Chicago area?

A. Yes.

Q. Who was the colleague that invited you to give the lecture?

A. Shing Chang.

Q. What other positions did you hold at Abbott after you were divisional vice president of cancer research?

A. I took on the position of divisional vice president of, I think it was called oncology development. As soon as I transitioned from drug discovery to

drug development, for a period, I had both accountabilities, and then, as I shifted to dominantly development, the title changed to reflect that.

Q. Were you divisional vice president of oncology development when you left Abbott?

A. Yes.

Q. So is it fair to say that when you joined Abbott as divisional vice president of cancer research, most of your responsibilities had to do with discovery?

A. Yes.

Q. And at some point in time, your -- your responsibilities changed so that you had more responsibility for development, is that right?

A. As the assets entered into the clinic, I followed them, given my training and experience, which was in both basic sciences and clinical medicine.

Q. Was one of those assets a

compound named ABT-518?

A. Yes.

Q. Did you work on ABT-518 when it was in the discovery phase?

A. Yes.

Q. And how many other compounds were among the assets that you helped manage from research into development?

A. I'll have to count. About a half a dozen.

Q. And can you briefly describe, again for us lay people, the difference between discovery and development as it pertains to the drug compounds?

A. Generally, drug discovery refers to the identification of the molecule that one then administers to people. Drug development generally refers to those studies and the conduct of studies in human beings to determine if those molecules are safe and effective in people. And there is a blurriness as an -- as an asset or a molecule goes

through later drug discovery and enters into the clinic.

THE VIDEOGRAPHER: Excuse me. Off tape, 9:19.

(Whereupon, a discussion was held off the record.)

THE VIDEOGRAPHER: Stand by, please.

Back on the record, 9:21.

BY MR. DAVIS:

Q. Dr. Nisen, have you ever testified under oath, other than the occasion when you were deposed?

A. Yes.

Q. Okay. On what other occasions have you testified under oath?

A. When I was a house officer at Columbia-Presbyterian, I testified in a murder case, actually, of a child who I took care of in the emergency room.

Q. Was that a trial?

A. Yeah.

Q. Have you testified in any other trials?

regulatory purposes that included various clinical dossiers and reports and summaries of material. I don't remember if there was a specific preclinical database or not.

Q. Were the -- were there teams at Abbott that were devoted to development of specific compounds?

A. Yes.

Q. So, for example, was there an ABT-518 team?

A. Yes.

Q. And if I refer to it as 518, you'll understand that I'm referring to ABT-518, is that fair?

A. Yes.

Q. Who was on the 518 team?

A. To the best of my recollection, Azmi Nabulsi, a physician lead, Diane D'Amico, as a project manager, or clinic -- I guess clinical operations activities.

Q. Um-hmm.

A. And there were other

program and I can't remember exactly who was involved when.

Q. Would Dr. Nabulsi have been responsible for helping to oversee any clinical trials of 518?

A. Yes, probably.

Q. Were you a member of the 518 development team?

A. I was in charge of overall development of all of the oncology assets. So to the extent that 518 was an oncology asset, I was involved as the head of that program. I was not -- I didn't lead the project team meetings, for example.

Q. Did you attend project team meetings?

A. Not in general, to my recollection.

Q. On occasion?

A. Possibly. I don't specifically remember. But not in general, to my recollection.

Q. Were there 518 team records

Q. In your capacity as divisional vice president of oncology development, to whom did you report?

A. John Leonard.

Q. What was his position?

A. I believe his title was vice president, development.

Q. How frequently did you report to Dr. -- it's Dr. Leonard, correct?

A. Do you mean how often did we meet?

Q. Well, is Mr. Leonard a doctor, to your knowledge?

A. Yes.

Q. How frequently did you meet or report to him regarding the status of projects that you were supervising?

MR. LORENZINI: Objection.

You can answer.

BY MR. DAVIS:

Q. You can -- if he objects, unless he instructs you otherwise, you can go ahead and answer the question.

Q. Was one of the assets that was reviewed in the course of that meeting, to the best of your recollection, 518?

A. Possibly, but I don't remember the specifics of what we talked about.

Q. You were aware before the research funding agreement between Hancock and Abbott was signed that such a deal was being negotiated?

A. Yes.

Q. How were you made aware of that fact?

A. I had, to my recollection, conversations with some of the business development people. Initially the head of R&D finance, whose name, Steve, I don't remember.

Q. Mr. Cohen?

A. Cohen, Steve Cohen, and Phil Deemer.

Q. Do you recall when it was approximately that you first became aware

of the -- of a potential deal between Hancock and Abbott?

A. No.

Q. Were you asked by Mr. Deemer or Mr. Cohen or anyone else in Abbott to provide any assistance or support in helping to make that deal happen?

A. I was asked to provide information about the assets, the oncology assets.

Q. What information were you asked to provide?

A. To my recollection, what we knew about it, what the target was, what the attributes of the asset were, how we were planning to develop it, what its development status was.

Q. Were -- was there more than one oncology asset that you reviewed or discussed with Mr. Deemer and Mr. Cohen in this context?

A. Yes.

Q. Which assets? Which compounds, if I can call them that?

A. We -- we likely reviewed all of the assets in or near clinical development in oncology at the time.

Q. Do you recall the numbers or designations for those particular assets?

A. I can do my best.

Q. That's all I can ask.

A. There was an endothelin receptor antagonist called ABT-627. There was probably an antimitotic compound called ABT-751. There might have been an angiogenesis inhibitor called ABT-510. Probably ABT-518 that we're talking about. And I think we had already terminated another molecule, which was ABT-839, which was a farnesyl transferase inhibitor.

I believe those to be the main ones.

Q. The ABT-627, was that also known as Xinlay?

A. Yes.

Q. And are you aware that some of the compounds that you discussed with

Mr. Deemer and Mr. Cohen ultimately were included in the basket of compounds that were encompassed by the agreement with Hancock?

A. Yes.

Q. And you knew that 518, for example, was going to be among the compounds included in the basket, is that correct?

A. I think so, yes.

Q. Among the activities that you engaged in before the agreement with Hancock was signed, did you assist in developing descriptive memoranda for any of the compounds?

MR. LORENZINI: Objection.

THE WITNESS: I don't remember specific descriptive memoranda, but I do remember being involved in providing information and data likely generated by others.

MR. DAVIS: Let's mark this, please, as Exhibit Number 1.

(Exhibit No. Nisen-1, Descriptive Memorandum, May 2000, Bates ABBT246447/246454, was marked for identification.)

BY MR. DAVIS:

Q. Dr. Nisen, you have what has been marked as Exhibit Number 1 at your deposition. I'm going to ask you to look at that document for a moment and tell me if you've seen it before, please.

A. I saw it yesterday with Eric Lorenzini.

Q. Prior to seeing it with Mr. Lorenzini, reviewing it with him yesterday, had you seen this document before?

A. I don't specifically remember whether I saw this document or not.

Q. Do you recall whether you assisted in any way in the development of any descriptive memoranda with respect to any oncology compounds for purposes of the Hancock deal?

A. I remember that I was asked to provide information about the assets that led -- I remember that I -- I contributed that information, various information, various other documents and various other information that summarized information about the assets.

I don't recall this particular document.

Q. The information that you provided in response to the request, did you create anything, did you create any new written documents, for example, or did you simply provide copies of existing documents?

A. I don't remember.

Q. And you, as you sit here today, do you know who created a descriptive memoranda for ABT-518, for example?

A. No.

Q. Do you recall reviewing drafts of descriptive memoranda for ABT-518?

(Exhibit No. Nisen-2, ABT-518 February 2001 Document, Bates ABBT0000343/0000348, was marked for identification.)

BY MR. DAVIS:

Q. Dr. Nisen, you have in front of you what has been marked as Exhibit 2. Would you tell me, please, if you've seen this document before?

A. I believe I saw this yesterday with Eric Lorenzini.

Q. Prior to reviewing this document with Mr. Lorenzini, had you seen this document before?

A. I don't remember the specific document.

Q. Had you seen documents in this format before?

A. Not that I can exactly remember. The challenge I'm having, to be clear, is five years ago, different company, two years intensively involved with this new company. It's very difficult for me to recall, or it's

impossible for me to recall explicitly certain documents of certain sorts.

Q. Well, we're going to look at a lot of documents here today, Doctor, and so I'm --

A. I'm going to do my best.

Q. -- I'm going to ask you as best you recall --

A. Yeah.

Q. Okay.

-- in each instance to tell me whether you've seen the documents before or whether you can recall reviewing either those specific documents or documents of that type.

I'll represent to you that this is a document produced to us by Abbott in this matter.

A. Um-hmm.

Q. That appears to be some sort of monthly report pertaining to ABT-518. And let me ask you whether, is it your -- is it consistent with your recollection that when you worked at Abbott, there

were monthly reports of some type generated within Abbott specific to particular compounds?

A. I -- yes, there were -- yes, I remember that there were regular summaries of assets following certain kinds of templates. I don't remember this specific one. I don't remember if this was the one used monthly or where it was used or to whom it might have been distributed, nor do I remember this particular document, although, I do recall reviewing documents of various sorts like it.

Q. Do you recall reviewing some sort of monthly reports concerning the compounds for which you were responsible?

MR. LORENZINI: Objection.

THE WITNESS: Could you be more specific?

BY MR. DAVIS:

Q. Sure.

In your capacity as vice president of -- the official title was

in -- there were these decision trees analysis -- decision tree analyses of the portfolio. I remember more involvement around that.

I don't remember who might have put together sort of this monthly, if there -- a monthly status update report. I'm sure there was a group doing that. I'm not sure. There was a likely group doing that. I cannot recall the details of who did it or how they did it or what the form was or to whom they sent it.

Q. Would you look at Exhibit 2 for a moment?

A. Yes.

Q. I want to ask you some questions about the actual subject matter --

A. Okay.

Q. -- that's identified in Exhibit 2. First with some basic questions.

What was or what is ABT-518?

A. It's a matrix meta -- metalloproteinase inhibitor. A -- matrix metalloproteinases are enzymes in the body that affect a lot of processes, including invasion -- the ability of cancer cells to invade and spread. And this molecule was selective for two of those metalloproteinases that seem to be particularly important in the invasion and spread of cancer cells.

Q. Is it fair to say that ABT-518 was a compound that Abbott thought might inhibit tumor growth in someone?

A. Particularly metastasis or spread.

Q. And that was the reason why Abbott was interested in ABT-518, is that correct?

A. Yes.

Q. And you said it's a metalloproteinase inhibitor. Is that group of compounds sometimes referred to as MMPIs?

A. Yes.

Q. So ABT-518 was an MMPI?

A. Yes.

Q. Did Abbott have other MMPI compounds under development while you worked there at any point in time?

A. No. We had -- there was a long-term drug discovery program leading to the generation of MMPI molecules for clinical investigation. 518 was the molecule that I remember that we entered into the clinic. We had other precandidates or candidates that fell down along the way because of either toxicologic findings or other information. This is the molecule I remember we entered to the clinic.

Q. Was there something particular or particular characteristics that caused you to enter this compound into clinical trials as opposed to others?

A. Yes.

Q. What were they?

A. So we were impressed by the selectivity of this inhibitor in contrast to many of the other MMPIs in development. The other ones more -- in more advanced stages of development were more pan inhibitors across that family of enzymes, and we thought that we might be able to achieve the benefit of clinical efficacy in cancer, targeting just those two enzymes and not have the liabilities with respect to safety that the pan inhibitors had, because they were causing joint toxicities and joint pain, so we thought it was a problem and limited the ability to administer those.

We were also impressed, to my recollection, with the pharmaceutical properties of the molecule was very potent and it had good bioavailability and good pharmacokinetics, meaning its exposure in the body. So we thought it had good drug-like qualities in addition to being a target that we thought and others obviously thought was an

interesting target for intervention for cancer.

Q. I'm trying to break down some of what you said --

A. Yes.

Q. -- so that ultimately non-physicians reading this material might understand it.

You said that you thought that you were impressed by the selectivity of it?

A. Yes.

Q. Meaning that you understood that 518, as best you could tell, targeted specific enzymes, is that correct?

A. Yes.

Q. Two in particular?

A. Yes.

Q. And you thought that the advantage to that was that by targeting just two enzymes, the -- some of the disadvantages that might have been observed in other MMPI candidates, for

example, joint pain, might not be present or might be present in a lesser amount if someone used 518?

A. Correct.

Q. In addition, I think you made some reference to that you were impressed by the pharmaceutical properties of it, that you thought it was, excuse me, I don't have the transcript in front of me, but you thought it was more efficacious?

A. I said that it was more potent.

Q. More potent.

A. Meaning that less could be given to inhibit the enzyme, that you could swallow the pill and it would be absorbed into the bloodstream, what we would refer to as bioavailability.

There's a fire drill at 10 o'clock.

Q. Yes. I -- I think we're entitled to sit through it, but I noticed on the way in this morning that there was

a sign up that there would be a fire drill at 10:00 a.m.

A. Right.

Q. So I am going to assume that they'll let us know if it's more than -- more than just the drill.

A. So you are not required to leave the building?

Q. Unless and until we're told, we're -- we're going to stay here.

A. Okay.

Q. Although you're free to leave if you wish to. I'm -- make sure that I'm not instructing you to stay here.

A. I'm enthusiastic that --

Q. My luck, the tape would be the one thing that survived.

Okay. You mentioned that you thought it was more --

A. Potent, bioavailable, so that it could be absorbed and stayed in the bloodstream for a period of time, so we thought those were important

attributes.

Q. Did you think that those were attributes that would -- were not necessarily demonstrated by other MMPI compounds?

A. We thought this would be potentially better -- that those properties would be better than the others.

Q. When you say the others, you mean MMPI compounds under development by other companies?

A. Correct.

Q. And was one of those other MMPI compounds marimastat?

A. Yes.

Q. Was a -- do you recall the names of any of the other MMPI compounds that were under development by other companies?

A. There was tanomastat. There was a Bayer compound. There was a Bristol-Myers compound. There were probably ten or so. An Agouron molecule.

There were at least ten matrix metalloproteinase inhibitors in development. There was a lot of interest in the scientific oncology community in this target.

Q. At least as of 2001, did you believe that 518 had potential advantages over those other MMPI compounds?

A. Yes.

MR. LORENZINI: Objection.

BY MR. DAVIS:

Q. Were you -- did you ever, in your own mind, prove or disprove whether that was, in fact, the case?

MR. LORENZINI: Objection.

THE WITNESS: Could you help me -- be more specific about your question?

BY MR. DAVIS:

Q. Certainly.

As of 2001, you had a belief that ABT-518 might have the advantages that you described of -- over other MMPI compounds, is that correct?

differentiate assets at -- in early Phase I. So I don't think it's answerable in early Phase I.

BY MR. DAVIS:

Q. Well, did this compound progress beyond Phase I?

A. No.

Q. And did Abbott continue to engage in clinical development of 518 for the purpose of determining whether the beliefs that you held regarding its potential advantages were correct?

MR. LORENZINI: Objection.

THE WITNESS: Can you help me understand your question a little better?

BY MR. DAVIS:

Q. Fine.

At some point in time, was clinical development of 518 terminated by Abbott?

A. Yes.

Q. When was that?

A. I don't remember exactly,

but at a point after, to my recollection, after the American Society for Clinical Oncology meetings in, I believe, May, I imagine that would be 2001 then, I think the collection of data, at that point in time, with regard to several presentations of competitor molecules, really led to the decision that the likelihood of success, given the lack of success with the other multiple molecules, targeting matrix metalloproteinase inhibitors, that they were all -- the body of negative evidence, I think the tipping point, was reached largely around then.

Q. Would it be fair to say that Abbott decided, based on information about other competing compounds, that it did not wish to pursue further development of ABT-518?

MR. LORENZINI: Objection.

But you can answer.

THE WITNESS: Could you try that again?

BY MR. DAVIS:

Q. Certainly.

Is it fair to say that Abbott decided not to further pursue the development of ABT-518 based upon information obtained regarding other competing compounds?

A. I remember that that contributed to the decision.

Q. Was it any particular information obtained during trials of ABT-518 that caused Abbott, to your knowledge, to cease development of that compound?

A. My recollection was that the real turning point for the decision about developing MMPIs was dominated by what seemed like at the time the overwhelming negative clinical evidence with other molecules.

Q. Not --

A. That were more advanced than ABT-518.

Q. If you'd look back on Page 1

necessary to conduct Phase I studies.

When one says -- I guess I'm struggling with your point of when Phase I began. So is it -- we generally refer to the initiation of all those activities as the initiation of Phase I. We might use as a metric when the first subject is actually dosed, but it's really a small part in the continuum of activities.

Q. To your recollection --

A. So there was commitment to conduct that work necessarily -- necessary to start. And I can't pick through dates of what started when and what Phase I means. And that -- there I'll have trouble to answer.

Q. When it says "Study will initiate October, 2000," what does that mean?

A. Well, I don't remember exactly what that means.

Q. You don't know what it means to initiate a study?

A. To initiate -- again, so to

initiate a study to me means conducting all that work coincident with starting, so drug product, toxicology, clinical -- a clinical -- creation of the clinical study, the clinic -- the dossier regulatory approval, ethics review board approval.

So there's a constellation of events. So it's those myriad that -- those myriad activities.

Q. To your knowledge, had Abbott elected or decided to fund a Phase I clinical trial of ABT-518 as of April 2000?

A. Again, I don't remember dates. My ability to recall specific dates, I can't do.

Q. Well, based on what you see in this document, is it your understanding that Abbott had elected or decided to fund a Phase I clinical study, at least as of this time?

A. Yes.

Q. And if you take a look a few

A. No. I meant pause.

Q. Do you recall -- do you recall some sort of directive or order coming from Abbott to people working on the trial that they should stop enrolling patients in that trial?

A. I remember that there was a request to pause activities. I don't remember the specifics.

Q. Who made the decision to pause activities in that trial?

A. I don't remember specifically, but likely involved John Leonard and Jeff Leiden.

Q. Do you recall Dr. Leonard and -- I think it's Dr. Leiden -- being involved in that decision?

A. I don't remember the specifics.

Q. Do you recall generally that they were involved in that decision?

MR. LORENZINI: Objection. Asked and answered.

THE WITNESS: I don't

A. Yes.

Q. And that would include 518?

A. Yes.

Q. And you mentioned that there were concerns around accumulating body of evidence regarding MMPIs, is that correct?

A. Yes.

Q. So the decision, to your knowledge, regarding the pausing of the 518 Phase I clinical trial had to do with both availability of resources to fund that development effort, but also concerns around information that was becoming known to Abbott regarding the fate or status of other MMPI compounds, is that right?

A. Probably. But I must be very clear, my recollections are vague and the time specifics I'm even more vague about. And I will not be able to share with you what was thought when exactly.

Q. But what I --

A. My -- my -- let me be clear. My -- my main recollection about concerns regarding efficacy of the class really came to a head after the -- and around that ASCO meeting in May. That's what I mostly recall. There was always accumulating data, but I do remember that a key inflection point, if you will, in terms of reasons to believe really in that, that -- after that ASCO meeting. That I mostly -- that's what I do recall.

As to the funding issues, and a pause, I've expressed to you the best that I remember what happened. I really don't remember the details. I don't remember if it was a -- if there was either a decision specifically there. But I do have -- you asked me my recollection, and my recollection is a flavor of -- of concerns always around inadequate resource to do all the studies we wanted to do as a general statement, which is, I think true for everybody pursuing clinical development in every

company with every molecule, frankly.

Q. Your recollection --

A. Yeah.

Q. -- around the reasons for the pause in the Phase I clinical study involving 518 has to do with the availability of resources, correct?

A. That's my vague recollection. But I'm really not sure.

Q. And -- but also --

A. Very vague. So if I could frame that as --

Q. All you can do is give us your best recollection.

A. Yeah. And that's --

Q. That is your best recollection here today, is that correct, that that was one of the factors in the decision to pause the Phase I clinical trial for 518?

A. I think so.

Q. And also one of the factors in the decision to pause the Phase I clinical study for 518, to the best of

expected or probable spending?

A. Not really.

Q. Do you recall within Abbott any differentiation between sort of nominal spending numbers and any expected or probable spending based on some sort of success ratio or --

A. Not really.

Q. No?

Were you ever called to differentiate between those two in coming up with planned spending numbers within Abbott?

A. Not to my recollection.

MR. DAVIS: Let's mark this, please, as the next exhibit, Number 5.

(Exhibit No. Nisen-5, ABT-518 Transition Strategy, Bates ABBT256634/256645, was marked for identification.)

BY MR. DAVIS:

Q. Dr. Nisen, you have what has been marked as Exhibit 5 at your

deposition. Would you look at this document for a moment and tell me if you can identify it for me?

A. It says a "Transition Strategy," and I have the vaguest recollection of creating something like that, but it's very, very vague. My recollection is very, very vague.

Q. We spoke a few moments ago, I think you testified a few moments ago about the process of transitioning a prospective compound from research or discovery to clinical development.

Do you recall that?

A. Yes.

Q. Does this tran -- did this transition memo, to your knowledge, play any role in the process of transitioning ABT-518 from research or discovery to clinical development?

A. Yes. I think it looks like it summarizes most of the coincident activities necessary.

Q. Did -- did you or did people

working for you develop this document?

A. Yeah. Probably.

Q. And to whom was this document presented or submitted?

A. I don't remember.

Q. Who, by name, as best you recall, within Abbott made the decision to move ABT-518 from research or discovery into clinical development?

A. My recollection was, there was a meeting called this DDC, that was generally attended by Jeff Leiden, Dan Norbeck, who was the head of drug discovery, John Leonard, and a few others, where approval was given that the team had successfully achieved the criteria necessary to proceed to transition.

And then a team were asked to then establish, I think around that time, I don't know if it was before, during it or after it, a transition strategy so as to enable what needed to be done next to get to, more or less, the

next decision point and enter into the clinic and do the studies necessary.

Q. What --

A. I don't remember when a document was prepared, to whom it was presented, nor the -- an approval process that went along with that.

Q. Do you recall approximately when it was that that meeting took place, the DDC meeting?

A. I'm sorry, I don't.

Q. Was it before or after August of 2000?

A. I don't remember, I'm sorry. Likely -- I don't remember.

Q. As you sit here today, do you have a recollection as to whether this document, Exhibit 5, was prepared before or after the DDC meeting?

A. Either at it or after it. Not before it probably.

Q. I just point you to some --

A. But I don't remember exactly, I must say.

Q. I'd like to point you to subsections of this document for a moment.

A. Okay.

Q. And just ask you about it.

If you turn to the second page of this document, under "Introduction and Background," the third paragraph down, it's the last two lines, states, "ABT-518" -- actually, watch me butcher this -- "ABT-518 possesses sub-nanomolar potency versus gelatinase B, an improvement of 200-fold over ABT-770."

First, did I butcher anything there?

A. No.

Q. Oh, good.

What does that mean?

A. It means it's a very, very potent molecule, so very little of it is needed to inhibit the enzyme, much less so than the predecessor compound. That's what sub-nanomolar is. That's

extraordinarily potent. And it's very selective. It says toward -- gelatinase B is one of the two enzymes we were most interested in, gelatinase A and gelatinase B.

So this is what that says.

Q. Is it fair to say that the more potent a compound is, the better that is in most circumstances, because you have to deliver less of the compound to the patient?

A. Generally.

Q. You -- you regarded it as a potential advantage of ABT-518, that it was more potent --

A. Yes.

Q. -- than ABT-770, correct?

A. Yes.

Q. The next sentence states, "ABT-518 is also a substantially more selective inhibitor of the gelatinases compared to prinomastat, suggesting that it may avoid mechanism-based joint effects."

Do you see that?

A. Yes.

Q. And that's a reference to the point I think that we made earlier today, which is that you thought that by selectively inhibiting these two specific enzymes, that ABT-518 might avoid some of the joint effects that were being seen with other MMPI compounds, is that right?

A. Yes.

Q. Again, you regarded that as a potential advantage for ABT-518, correct?

A. Yes.

Q. Now, the next line says, "In animal tumor models, ABT-518 demonstrated anti-tumor activity equal or superior to ABT-770 and prinomastat."

Do you see that?

A. Yes.

Q. Okay. At this point in time, did you think that ABT-518 was likely to be more efficacious than some of the other MMPI compounds that were

under development?

A. Yeah. Or at least as good as, yeah.

Q. If you take a look at Page 4 of this document, you see there's a chart there that says "MMP Inhibitors in Advanced Clinical Development."

Do you see that?

A. Yes.

Q. And one of them is marimastat, which we've discussed earlier today, correct?

A. Yes.

Q. And do you recall that was under development by British Biotech?

A. Yes.

Q. And then we also see prinomastat, which was under development by Agouron and Pfizer.

Do I have that correct?

A. Um-hmm.

Q. Near the bottom of that page, there's a reference to competition in the field for MMP inhibitors?

A. Yes.

Q. It says that it was a compelling successor. What did that mean? In what way was it compelling?

A. Just that. Just the particular use of language in that document. I think you -- what you read, I think, summarized accurately the view that was held by most people, that with a highly selective inhibitor, that one could achieve efficacy. And, in part, the reason one could have reason to believe that one would achieve -- expect to achieve efficacy is that without the joint effects possibly caused by touching those other enzymes, you'd be able to continue to give this stuff so that it might be able to work.

So the selectivity being able to achieve -- enable the continued administration of the drug, where those others, you had to pause or stop because it had those untoward effects. So I think this summarized accurately the

view.

MR. LORENZINI: Could we take a break? Is there a problem with the microphone?

THE VIDEOGRAPHER: I've just got five minutes left on tape.

MR. DAVIS: Okay. That's fine. Thank you.

BY MR. DAVIS:

Q. Is it fair to say, Dr. Nisen, that you understood that one of the potential advantages of ABT-518 was that if it could avoid the joint effects, that patients who were taking 518 would be able to continue to receive the drug for longer periods of time and there hopefully -- therefore, hopefully benefit from the drug for longer periods of time than they would be if they took another MMPI?

A. That was an hypothesis.

Q. Was that hypothesis ever proven or disproven by Abbott?

A. It was never proven by

conducted anywhere other than in the Netherlands?

A. No.

Q. How did it come about that Abbott chose to do that study in the Netherlands?

A. We had good relationships with investigators there. We thought they did high quality studies and speed, they had a favorable regulatory and ethical review process. So we thought we could be more prompt, timely in our studies, conducting quality studies there.

Q. It says, "We will likely file a US-IND first quarter '01."

Did, in fact, Abbott file a US-IND for 518?

A. I don't remember.

Q. Were IND filings among the materials that you would expect Abbott to maintain in its regulatory files for 518?

A. Yes.

Q. And was -- had, to your

don't recall specifically, and then I can follow up with a question about whether you have a general recollection. But what I'm trying to get at is whether you have any recollection, specific or general, when I ask these questions.

Do you understand that?

A. Yes, I do.

Q. Okay. And so my question I guess is, do you have any recollection, either specific or general, of criticizing or calling into question sales forecasts with respect to compounds in Abbott's oncology portfolio?

A. I remember thinking they were always a billion dollars no matter what. I'm being facetious. No. The answer is no.

MR. DAVIS: Let's mark this as the next exhibit.

(Exhibit No. Nisen-10, ABT-518 Descriptive Memorandum, February 2001, Bates ABBT0004032/0004039, was marked

for identification.)

BY MR. DAVIS:

Q. This is Exhibit 10. Dr. Nisen, I'm going to show you what's been marked as Exhibit 10 at your deposition and ask you if you've seen this document before?

A. Isn't this what you showed me earlier?

Q. Well, actually, I think, sir, this is a different version of a descriptive memo for ABT-518. I believe that the document that you're referring to is Exhibit 1, and that is a document dated from May 31st, 2000.

A. I see.

Q. Or May of 2000 for the meta -- matrix --

A. Yes, I see that. I don't remember the specific document.

Q. Have you seen this document before?

A. I saw a document, and I don't remember if it was this one or

BY MR. DAVIS:

Q. And you can't give me any more information than you've already provided, correct?

A. No.

Q. What I said is correct? What I said is correct, you cannot give me any information beyond what you've already provided, is that right?

A. I don't -- I guess not. I've tried to answer your question as best I can.

Q. And I've tried to address your concerns the best I can. I don't know, within the confines of the English language, how I can make it any clearer. So I guess we'll have to move on and revisit that, if necessary, with the court.

All right. If you look on the bottom of Page 2 onto Page 3, the paragraph that begins, "ABT-518 displays no meaningful effects in genotoxicity."

Do you see that paragraph?

A. Yeah.

Q. Would you read that paragraph to yourself and tell me when you're done?

A. Okay.

Q. You see that there's a reference there to, again, to "ABT-518 is therefore a compelling development candidate with the potential to demonstrate anti-tumor effects superior to the MMP inhibitors currently undergoing clinical trials."

Do you see that?

A. Yeah.

Q. Do you -- did you believe that to be true as of February 2001?

A. Yeah.

Q. Did you believe it to be true as of March 2001?

A. I'm unable to distinguish for you what I believed in February versus March versus April versus May.

Q. At some point in time, did you come to believe that ABT-518 was not

shortcomings of the competitive products provide an opportunity for a compound with an approved SE or efficacy profile."

What is SE?

A. I'm not sure. Probably -- I'm -- probably safety profile, but I don't know what SE stands for.

Q. It goes on to say, "Current animal models seem to predict Abbott's compound is superior to those currently in clinical trials, and has the potential to be best in class."

Do you believe that that was accurate as of February 2001?

A. Yes.

Q. And what does it mean to be best in class?

MR. LORENZINI: If you understand.

THE WITNESS: I think best means best.

BY MR. DAVIS:

Q. In what way?

A. I think any assessment of

any molecule is that clinical benefit ratio of benefit in the context of untoward effects, so that best ratio of working and untoward effects being better than the others.

Q. And did you believe at that point in time that if that was the case, that ABT-518 would have an advantage in the marketplace over other compounds, other MMPI compounds?

A. Yes.

Q. If you look at Page 6 of the document, under "Marketing overview," there's a section titled "Side Effects."

A. That's what SE must refer to, then.

Q. SE refers to side effects?

A. Probably.

Q. If you read that paragraph to yourself and tell me when you're done, please.

A. Okay.

Q. The last sentence in that paragraph says, "As a critical Go/No Go

And I take it that there were no final indications from any of those studies, because Abbott never conducted them, correct?

A. Correct.

MR. DAVIS: Okay. Stop here for lunch?

MR. LORENZINI: Sure.

THE VIDEOGRAPHER: Off tape, 12:16.

(Luncheon recess is taken from 12:16 p.m. until 12:54 p.m.)

THE VIDEOGRAPHER: Stand by, please.

Back on the record, 12:54.

MR. DAVIS: Can you mark this, please, as the next exhibit?

(Exhibit No. Nisen-11, Abbott Portfolio Review, March 7-9, 2001, Bates ABBT0013224/0013232, was marked for identification.)

BY MR. DAVIS:

Q. Dr. Nisen, you have what has

been marked as Exhibit 11 to your deposition, and I'm going to ask you if you've seen this document before?

A. Yesterday.

Q. Now, when is the last time -- had you seen it before yesterday?

A. Not that I really remember specifically.

Q. Do you have any general recollection of seeing this document before yesterday?

A. General recollection, yeah.

Q. Do you recall participating in an Abbott portfolio review on -- in or about early March 2001?

A. I can't remember the specific meetings that I participated in in 2000 --

Q. Do you have any recollection of those meetings?

A. Yes.

Q. Do you --

A. Of review meetings, yes.

Q. Okay. Do you have any

Q. But what did you -- you said there was a pause in enrollment.

A. For like a day or something.

Q. Do you recall what other effects there were, if any, as a result of the pause or the hold?

A. No. Other than having to call the investigator, I assume.

Q. Did you speak with any of the investigators about the pause or the hold on the 518 clinical trial?

A. No.

Q. Miss D'Amico goes on to state in her e-mail, "The next day we learned that the hold had been lifted."

A. Um-hmm.

Q. Again, I'll represent to you that Monday of this week was March 12th, 2001, and that the next day would have been March 13th, 2001, and that was the day on which the John Hancock/Abbott research funding agreement was signed.

To your knowledge, was the decision within Abbott to lift the hold

on the Phase I clinical trial of ABT-518 related in any way to the deal between John Hancock and Abbott?

A. Not to my knowledge.

Q. Who made the decision to lift the hold on the Phase I clinical trial of ABT-518?

A. I don't remember.

Q. Did you make that decision?

A. No.

Q. Did you have the authority at that time to make that decision?

A. I don't remember. Probably not.

Q. Do you recall learning at that point in time that someone had made a decision to lift the hold?

A. Not beyond reading what I read in the documents recently.

Q. So you have no independent recollection of the hold being lifted?

A. I think so. It's hard -- I can't separate from you independent recollection from having read this just

now, frankly.

Q. As best you can, Doctor, I'm going to ask you to tell me what you recall from your memory as opposed to what you've read in the documents concerning the lifting of the hold on the Phase I clinical trial of ABT-518.

What do you recall?

A. That we continued with development and enrolling subjects and carrying on as planned.

Q. Do you recall learning at some point in time, back in the 2001 time frame, that the hold had been lifted?

A. Very, very vaguely.

Q. Do you recall doing anything to determine why it was that the hold was lifted?

A. No.

Q. Did you ever learn, even if you don't recall right now, did you ever learn in that time frame why it was the hold had been lifted?

A. No.

bottom e-mail from Mr. Deemer on or about March 20th, 2001?

A. No, I don't remember it.

Q. Do you recall writing the top e-mail to Mr. Deemer on or about March 21, 2001?

A. I don't recall the specific e-mail, but the points in there are of -- are things I would have said. Some of them are personal.

Q. I'm not going to ask you about all of it. There are some pieces of these e-mails that I want to question you about.

A. Sure.

Q. First, Mr. Deemer wrote to you on March 20th, "You probably heard that Hancock was signed last week $214,000,000 over 4 years! A long time coming but finally done. We had a little scare at the end when it looked like 518 was being slowed down which could have been the deathnell to the deal. I worked with John to protest that and I

understand it is back on track."

Do you see that?

A. Yes, I see that.

Q. Do you recall having any discussions with Mr. Deemer about the subject matter in that e-mail?

A. No.

Q. When you received this e-mail from Mr. Deemer, do you recall understanding what he was referring to when he said it looked like 518 was being slowed down?

A. No. I don't recall.

Q. Do you have an understanding as to why slowing down 518 could have been the death knell to the deal between Abbott and John Hancock?

A. No.

Q. And then you -- did you have an understanding as to who John was that Mr. Deemer said he worked with to protest that?

A. I presume John Leonard.

Q. Did you ever have any

discussions with John Leonard about the subject matter of this e-mail?

A. Not that I remember.

Q. Did you understand what Mr. Deemer was referring to when he said that it -- it is back on track?

A. No. I mean, I assume it's back -- no more than what that says.

Q. Then you wrote in return, on the following day, "Phil, mega mazel tov! You are the most tenacious guy I know - you deserve a new car not just a pen. I know all about the 518 debacle (I tell you more over the phone)."

First, let me stop and ask, did you ever have that telephone discussion with Mr. Deemer?

A. I don't remember.

Q. And -- and what did you mean, Dr. Nisen, when you referred to the 518 debacle? What was the 518 debacle?

A. I know. I don't remember.

Q. What do you regard as a debacle, what do you understand to be the

meaning of that term?

A. I tend toward hyperbole in my e-mails, and you can see it from this e-mail. So I think that's all that that meant by that, which was kind of an overstatement of some frustration.

Q. My question is slightly different, which is, what do you understand to be a debacle? How would you define that term?

MR. LORENZINI: Objection. Objection.

THE WITNESS: How do I define its use in the English language or what did I intend in this e-mail?

BY MR. DAVIS:

Q. I'm going to first start with your understanding of the meaning of that term as it's used in the English language.

A. It's --

MR. LORENZINI: Objection.

THE WITNESS: I think that's

germane.

Q. What data were presented at ASCO -- ASCO that caused -- you believe caused Abbott to terminate the development of ABT-518?

A. I don't remember the details. I do recollect that there were a series of negative studies across a series of molecules. I think around ten or so reports of negative kind of findings.

Q. Did they include negative results regarding marimastat?

A. I don't remember the details, but probably.

Q. And how about, is it prinomastat?

A. Again, probably, but I don't remember.

Q. Some of the information that you received, you heard at ASCO, was information that you knew about or had learned about prior to the ASCO conference, correct?

A. No.

MR. LORENZINI: Objection.

BY MR. DAVIS:

Q. None of the information that you heard at ASCO was information that you had learned before?

A. No. There's no information presented at the ASCO meeting that's presented -- if presented before the meeting wouldn't be eligible for presentation at that meeting.

Q. Well, you knew, for example, back in February of '01, that the development of marimastat had been terminated, correct?

MR. LORENZINI: Objection.

Asked and answered.

THE WITNESS: I actually, again, remember the details, but if there was a press release, I think you showed me one earlier today that said that. So what was publicly available was publicly available. I can't recall what

the next exhibit.

(Exhibit No. Nisen-31, Memo, 8/10/01 on Abbott letterhead, Bates ABBT0049970/0049977, was marked for identification.)

THE WITNESS: Are you accusing me of lying? Is that what you're saying?

MR. LORENZINI: You don't need -- you don't need to respond.

THE WITNESS: Well, let me state on your record that I've not been lying, that I don't lie and I resent what I think was an inference that I am.

MR. LORENZINI: I'm sure it's unintended.

MR. DAVIS: I'm not going to speak on your behalf, don't speak on mine.

BY MR. DAVIS:

Q. Dr. Nisen, Exhibit 31 is in front of you. Have you seen that document before?

A. I don't remember the specific document.

Q. Do you recall that after the decision was made within Abbott to terminate further development of ABT-518, you and some others within Abbott attempted to convince Abbott's management to resurrect the development of ABT-518?

A. I remember that Steve Davidsen, who was the discovery project leader, had strong views about trying to keep that alive. This is something that he worked on for almost a decade. And I remember that I thought we should follow -- finish up the study through, as stated in my other e-mails.

Q. And do you recall that you made recommendations to Abbott's management that they resurrect the development of ABT-518?

A. I don't remember resurrect, but in the e-mails that you showed me, its stated pretty clearly what my views were, I think, that I thought we should

finish that study.

Q. My question is a bit different.

Do you recall after Abbott decided to terminate the development of ABT-518 in or about May or June of 2001, that you and others within Abbott made an effort to convince -- convince Abbott's management to reverse that decision and to reinstitute, to recommence the development of ABT-518?

A. I don't remember specifically.

Q. Do you recall receiving this memo from Dr. Davidsen?

A. I think you asked me that and I said I didn't remember exactly receiving this document, but I do recollect discussions with him, reasons to believe and reasons to try to convince others that we should continue trying to develop the drug.

Q. If you take a look at the page of this Exhibit 31 that's numbered

in the lower right-hand corner that ends in 49976, you see it says, under "Conclusion," it says, "To conclude, we feel that ABT-518 has the potential to be the first MMP inhibitor to demonstrate robust clinical efficacy. The points listed below provide a compelling argument as to why the development of ABT-518 should be continued."

Do you see that?

A. Yes.

Q. Did you agree with that statement at that point in time, as of August, 2001?

A. I don't remember what I specifically agreed to or generally agreed or disagreed with. These were the views that he expressed strongly and that he believed strongly.

Q. Did you pass his views along to Abbott's management?

A. I believe I did.

MR. DAVIS: Let's mark this as the next exhibit.

(Exhibit No. Nisen-32, Interoffice Memorandum, 8/14/01, Bates ABBT0049980/0049981, was marked for identification.)

THE WITNESS: Albeit in a more succinct way, I imagine.

BY MR. DAVIS:

Q. You have in front of you Exhibit 32. Have you seen this document before?

A. I saw it yesterday.

Q. Is this a memo, an interoffice memo that you sent to Mr. Norbeck and to Dr. Leonard?

A. Yeah.

Q. Is -- by the way, who is Mr. Norbeck?

A. That's -- Dr. Norbeck was -- is the head of drug discovery at Abbott.

Q. When you sent this memo to Dr. Norbeck and to Dr. Leonard, were you hoping that they would recommence development of ABT-518?

A. I think I would have liked

to -- yeah, I think I would have liked to have seen us finish that study or find other ways to keep it alive.

Q. The very first line of the memo says, "Dan asked me to send" along -- I'm sorry.

"Dan asked me to send information that might convince him to revisit the decision regarding ABT-518 development?"

Do you see that?

A. Yes.

Q. Did you want Dr. Norbeck to revisit the decision regarding the development of ABT-518?

A. I don't remember what my desires were specifically. But probably.

Q. Do you recall generally?

Did you believe that the arguments that Dr. Davidsen was making in his memo of August 10th were valid?

A. Yeah.

Q. And you believe they were valid even after you had seen the ASCO

data, right?

A. I think you're asking me about two, two unrelated. So do one set of results mitigate another set of results? There are positive and negative findings. So, are you asking me, on balance, did I think then that, on balance, it made more sense to continue development and finish the study?

Q. Well, the ASCO conference that you attended was in May of 2001, correct?

A. Yeah.

Q. And even after the ASCO conference, you agreed with Dr. Davidsen that ABT-518 had the potential to be the first MMPI inhibitor to demonstrate robust clinical efficacy, correct?

A. That's what Steve Davidsen wrote. And I believe that my view is I would have liked to have seen that study finish, and if there was a way to continue its development, I would have liked to have seen that.

Q. So you thought that even in the light of the ASCO data, that it made sense for Abbott to continue the development of ABT-518, correct?

MR. LORENZINI: At this time?

MR. DAVIS: At this time.

MR. LORENZINI: August 2001.

THE WITNESS: What I said there was, completion of that Phase I study would enable us to confirm that we can achieve exposure safely without events and that a small study could be performed to establish proof of principle. So I think that reflects what I believed at the time.

BY MR. DAVIS:

Q. Well, the very first sentence of your memo says, you're sending the information to Dr. Norbeck to try to convince him to revisit the decision regarding ABT-518 development.

And my question is, that you think more likely than not, you would have sought out the answer to that question back in the March 2001 time frame, correct?

A. I think so.

Q. Did you ever make any efforts to obtain funding for further development of ABT-518 outside of Abbott?

A. I think so, yeah.

Q. What did you do?

A. We had one meeting with a philanthroper, this guy Bill Goodwin, looking at alternative means for investment in assets, where he was looking to invest in cancer research in maybe some unique ways.

And I think we explored with him, Jeff and I, Leiden and I did explore with him whether he might fund translational experimental medicine research with Abbott molecules at academic institutions, and we might have included 518 in that mix.

Q. When did you have those discussions with Mr. Goodwin?

A. I don't remember exactly when.

Q. It was after Abbott had decided to terminate development of ABT-518, is that right?

A. Probably, but I don't really remember when I met with him.

Q. Was it after you had attempted to get people within Abbott to revisit the decision to terminate the development of 518?

A. I don't remember.

Q. What was -- it's Mr. Goodwin?

A. (Witness nodding head.)

Q. What was Mr. Goodwin's response to your proposal?

A. He was not at all interested in the details of one molecule versus another, but the concept of how he might invest in cancer research in a unique way. And that was the focus of our

Q. That's where you would go?
A. Yes.
Q. Who is Miss Lebold, by the way?
A. She was in business development. I don't know what her current position is.
Q. As you sit here today, do you recall any material transfer agreement having been signed with Vanderbilt concerning ABT-518 while you were employed at Abbott?
A. I don't know. Vaguely, maybe. I don't really remember. I don't remember.
Q. This e-mail leads you to believe that there was one, correct?
A. Yeah, seems like it.
MR. DAVIS: Let's mark this as the next exhibit.
(Exhibit No. Nisen-37, E-mail string, 9/23/02, Bates ABBT334838/334841, was marked for identification.)

BY MR. DAVIS:

Q. Dr. Nisen, you have in front of you Exhibit 37, which are some e-mails, and attached to the e-mails is a project overview for ABT-518.

Have you seen these documents before?

A. No, not that I remember.

Q. Did you participate in any out-licensing activities regarding ABT-518?

A. I was probably asked for information and helped provide a package and a dossier, and if I knew anybody that might be interested.

Q. You recall doing that?

A. Only in the vaguest way. But I think I did.

Q. When you worked at Abbott, did you ever participate in any in-licensing activities?

A. Yes.

Q. How many occasions?

A. I struck some -- a couple

THE VIDEOGRAPHER: We're back on the record. This is the beginning of Tape 4. The time is 4:11.

BY MR. DAVIS:

Q. Dr. Nisen, did Abbott out-license ABT-518 while you were employed at Abbott?

A. No.

Q. Why not?

A. I think it's very hard to out-license drugs.

Q. What efforts, if any, do you know of that Abbott made to out-license ABT-518?

A. I think they shopped it to a lot of different companies, actually.

Q. How do you know that?

A. I just remember vague discussions of them going around and trying.

Q. Who did it? Who made those efforts?

A. I don't remember who was in

charge of business development then.

Q. Who did they talk to?

A. You're going to have to ask them who they spoke to.

Q. And what responses did they receive?

A. Again, you're going to have to ask them, but I think, in general, it's been -- I think that field has really been shut down as an area of investigation, and I think there's just no enthusiasm in the medical/scientific community for MMPs as a therapeutic intervention in cancer anymore.

Q. That's your understanding?

A. Yes.

Q. Are you still -- do you still follow that field?

A. No. Not closely.

Q. Did you have any -- do you know anything more about Abbott's out-licensing efforts with respect to ABT-518, other than what you've now told me?

some questions, but we need to pause for a minute. Can we take a break?

THE VIDEOGRAPHER: Off tape, 4:13.

(Recess is taken from 4:13 p.m. until 4:18 p.m.)

THE VIDEOGRAPHER: Stand by. Back on the record, 4:18.

- - -

EXAMINATION

- - -

BY MR. LORENZINI:

Q. Dr. Nisen, could you turn to Exhibit 10, please.

A. Got it.

Q. This is the descriptive memorandum dated February 2001 for ABT-518 that you reviewed previously.

A. Yeah.

Q. Did you have an opportunity to review this document in preparation for your deposition?

A. A little bit yesterday and

read through it again today.

Q. So you're familiar with the -- the contents?

A. Yes.

Q. Based on everything you know today, do you believe Exhibit 10 to be a complete and accurate summary of the status and prospects of ABT-518 as of March 2001?

A. Yes.

MR. DAVIS: Objection.

You can respond.

THE WITNESS: Yes.

MR. LORENZINI: I'd like to mark as a new exhibit number --

THE WITNESS: Maybe I'll just add, there are a mountain -- there is a mountain of information about MMPIs, positive and negative. In aggregate taken together, I do believe this is an accurate representation of the molecule and the state of affairs in the field at the time. To be

comprehensive, would have been a telephone book or more.

BY MR. LORENZINI:

Q. But you believe this to be a comprehensive summary --

A. Accurate --

Q. -- of the -- the relevant information?

A. I really do, yes.

(Exhibit No. Nisen-38, E-mail, 5/22/01, Bates ABBT0064226, was marked for identification.)

MR. LORENZINI: Why don't we just -- let me take that back for a second. I'll just show it to you, Brian, for a second.

MR. DAVIS: Thank you.

BY MR. LORENZINI:

Q. Dr. Nisen, you have before you what the court reporter has marked as Exhibit 38. Could you just take a moment to review this document, please?

A. Okay.

Q. I'll just state for the record this appears to be a May 22nd, 2001 e-mail from Perry Nisen to John Leonard with an attached document entitled ASCO 2001 MMPI update.

A. Right.

Q. Dr. Nisen, do you recognize this document, the e-mail and the attachment?

A. Vaguely now.

Q. Do you think this is an e-mail and attachment that you sent to John Leonard?

A. Yeah. I mean, it says it was from me. I have no reason to think I did not. No specific recollection of the document, but...

Q. Did you attend the ASCO conference in 2001?

A. You know, I can't remember if I was there myself or not. Probably.

Q. Whether you were there personally or not, do you remember getting results regarding competitors'

drugs at the 2001 ASCO conference?

A. Yeah, from -- from the conference.

Q. And does the attachment that's part of Exhibit 38 provide a summary of what you recall basically being the presentations from the ASCO conference?

A. I have no reason to believe they're not accurate.

Q. And you testified earlier that you recalled some negative information regarding competitor MMPI compounds being released at the 2001 ASCO conference in May --

A. Yes.

Q. -- of 2001.

Does this attachment that's part of Exhibit 38 provide a fair summary of the negative information that you recalled receiving from the ASCO conference?

A. Yes.

Q. And what -- what was it

about the findings that were presented at the May 2001 ASCO conference that you believe to be negative?

A. I think the totality of the negative findings, so ten abstracts, all basically negative as to efficacy and some increasing evidence of toxicity. But most important, I think, was just added to the body of negative evidence for lack of efficacy.

Q. And were these ten abstracts presented for the first time at the ASCO conference in May, to your knowledge?

A. Yes.

Q. These abstracts weren't something you reviewed prior to the conference?

A. Could not have. So by definition, to be accepted for presentation at ASCO is predicated upon the agreement that they -- those data will not have been -- would not have been presented elsewhere prior. They're pretty careful about that.

Q. And so the information from the ten abstracts that's summarized in this presentation was new information that was not available to Abbott prior to the ASCO conference in May 2001?

A. Correct.

MR. DAVIS: Objection.

THE WITNESS: Correct.

BY MR. LORENZINI:

Q. And you testified earlier that the decision to terminate ABT-518 in either late May or early June was related in some way to the new information that was made available at the ASCO conference in May, is that correct?

A. I think influenced by it. And that was, I think, part of the aegis to communicate these data. I think everyone was anxious to see what the new data and findings were, recognizing that there were a lot of clinical studies underway with competitor molecules.

Q. So the information contained in Exhibit 38 from the ten abstracts,

that was not available in -- not available to Abbott in March 2001?

MR. DAVIS: Objection.

THE WITNESS: I don't think they were available to anybody.

MR. LORENZINI: I'd like to mark a new exhibit.

(Exhibit No. Nisen-39, E-mail string, 5/28/01, Bates ABBT0033486/0033494, was marked for identification.)

BY MR. LORENZINI:

Q. Dr. Nisen, you have before you what's been marked as Exhibit 39. It's an e-mail from Diane Bronson to Diane D'Amico dated May 28th, 2001, with an attached document entitled "ASCO 2001 MMPI Update."

A. Okay. Looks like the same thing that we just looked at.

Q. Right.

A. The attachment is.

Q. Do you recall that we looked at an e-mail chain before that Mr. Davis

showed you that was similar to the e-mail chain -- that included the e-mail chain that's now been marked as Exhibit 39?

A. Yeah.

Q. And -- maybe we should turn back to that.

A. And I remember that it was a partial -- it was two or three of those slides, but not the complete slide deck.

Q. The earlier exhibit that Mr. Davis showed you?

A. Yeah, I remember that.

Q. And does this appear to be the complete attachment to the e-mail that you received?

A. Yes.

MR. DAVIS: Objection. You're asking if he recalls whether this is the complete attachment or you're just asking whether he can, looking at it now, he's making that judgment?

BY MR. LORENZINI:

Q. Well, first I'll ask, do you

recall this attached multi-page presentation?

A. No, not really.

Q. But you recall generally a presentation being prepared regarding the ASCO findings?

A. Vaguely, given my e-mail.

Q. All right. And you -- on Exhibit 39, there's an e-mail, May 22nd, 2001, from you to Azmi Nabulsi attaching ABT-518 slides.

Based on your review of this e-mail and the attachment that's been marked as Exhibit 39, do you believe this to be a complete set of the attachments?

MR. DAVIS: Objection.

THE WITNESS: Seems --

MR. DAVIS: You can respond.

THE WITNESS: Seems like it.

BY MR. LORENZINI:

Q. If you'll turn to the last page of Exhibit 39, there's ABT-518 development recommendations.

Do you recall recommending

continuation of the Phase I clinical trial in late May?

A. I think so. I think this probably does reflect my consistent personal view that we should see the study through, that we should complete the Phase I study, that we should get a target dose, stop it if there was toxicity, stop if there was -- basically stop for toxicity and that there was a small proof of concept, proof of principle study that we could still do. I still --

Q. Why did you believe at that time that -- strike that.

Why were you recommending that approach in late May of 2001?

A. It's hard to remember exactly where I was and what I felt at the time, but, again, it just seemed like my responsibility. And I felt as the advocate for this asset, that -- to always look for a path forward to see if there was something there, to still look

for a way forward.

Q. So the ASCO findings were negative, but you believed there was potentially some ability of ABT-518 to distinguish itself from the competitor compounds?

MR. DAVIS: Objection.

You can respond.

THE WITNESS: I think, again, in the absence of efficacy, I think what this reflects is a statement of maybe there's still a path forward to be able to demonstrate some signal of activity, even in the face of those fairly large negative other studies. At one point, one says enough already is hard to say. In the retrospect, it's easy, I think at that moment of time.

BY MR. LORENZINI:

Q. And management at Abbott terminated ABT-518 development soon after the ASCO studies were released?

A. I think so. I think that was the timing.

(Exhibit No. Nisen-40, E-mail string, 6/11/01, Bates ABBT0063625, was marked for identification.)

BY MR. LORENZINI:

Q. Dr. Nisen, you have before you what's been marked as Nisen Exhibit 40. It's an e-mail chain beginning with a June 11th, 2001 e-mail from you to Steven Davidsen.

Do you recognize this e-mail chain? Is this an e-mail that you wrote in June 2001?

A. Looks like it, yeah.

Q. And do you recall receiving some data from Steven Davidsen regarding the -- the clinical trials of ABT-518?

A. Yeah, vaguely, in that they were good exposures.

Q. What do you mean by "good exposures"?

A. Good exposure meaning you

can measure it in the blood and it lasted there from even those few subjects treated.

Q. What is the benefit of that?

A. As opposed to not having exposures, so that it was -- you took it, it got absorbed, it was there in the blood, it stayed in the blood. And that, to the question that was asked of me earlier with respect to metabolites, this measures a bunch of the metabolites. And one sees, in fact, that the parent drug exposures are higher and that there is -- don't seem to be gigantic amounts of metabolites over time and accumulate -- or accumulating, and actually much less than the parent drug.

So while there were statements and concerns regarding metabolites, and the question was asked, was there evidence that it wasn't allowed to be seen through to answer that. There are pretty good data here that you can measure those metabolites, many of them.

And they look pretty level, much lower than the parent drug. It's a log -- a log scale rendition of those data, so --

Q. If you look at Mr. Davidsen's June 11th e-mail to you, the second one down, he states, "Perry, this data ain't bad...damn near target exposure with 25 milligram dose. Metabolites are low at 22 days, no apparent induction of metabolism. Independent of whether ABT-518 is pursued further, I think it's safe to say that the decision to take it into clinical studies was not stupid..."

Was it -- maybe I'll read also your response. In response, you say, "Damn right."

Was it your belief at this time, as of June 11th, 2001, that Abbott's decision to take ABT-518 into Phase I clinical development was a smart decision?

A. Yes.

Q. And that's because you

believed at the time that it was taken into Phase I clinical trials that it had promise?

A. For the right reason, and I had said earlier that it seemed like -- and in that document, that summary, I referred to favorable pharmaceutical properties. And I think these data affirm that, that it had really good pharmaceutical properties, that it got into the blood. And even at the doses, the first doses we gave, achieving exposure in the blood, quite near what we thought you needed to have, is what we targeted to have, which is very encouraging. And that its half-life was good, so it stayed there. And that there weren't those metabolites that were of concern from the preclinical data.

So this provided human clinical evidence that you -- approximately, what a proper dose was, that it would achieve those exposures, that there wasn't metabolism -- that

there was some metabolism, but not the untoward kinds of metabolism that people were concerned about.

So it actually already answered a lot of questions that could be answered from that kind of a Phase I study. Perhaps luckily it did.

MR. LORENZINI: I have no further questions.

MR. DAVIS: Okay.

- - -

FURTHER EXAMINATION

- - -

BY MR. DAVIS:

Q. Dr. Nisen, I want to make sure I have your testimony correct.

You've now reviewed Exhibit 10, which is the February 2001 descriptive memo for ABT-518.

A. Yes.

Q. And it's your testimony, if I have it correct, that this is a comprehensive and accurate description of the status of that compound as of March

Color Key to Deposition Designations

Designation by Plaintiffs

Counter Designation by Defendants

Designation by Defendants

2

February 2001 — ABT-518

Feb-01 — **ABT-518 Matrix Metalloproteinase Inhibitor**

Franchise	Dev. Status	Brand Name	Generic Name	Patent Exp.	Indication(s)
Oncology	Phase I	TBD	TBD	2018	Solid tumors such as breast, non-small cell lung, ovarian and colorectal cancers; non-Hodgkin's lymphoma

Description

ABT-518 is a metalloproteinase inhibitor that selectively targets MMP-2 and MMP-9, metalloproteinases that have been implicated in the progression of cancer.

In preclinical studies, ABT-518 inhibits tumor growth in a variety of murine tumor models when administered alone, or acts synergistically with cytotoxic agents. ABT-518 also blocks blood vessel formation in a murine angiogenesis model.

	Unit	Value	CAGR 00-05	Unmet Need/Key Market Drivers	Key Competitors/Position to Market
U.S. Market	TRX	NA		Despite major advances in our understanding of the molecular events that underlie cancer, this disease remains the second leading cause of death in the US, with more than 550,000 cancer deaths last year alone. Today, advanced cancer is primarily treated with a combination of cytotoxic agents that typically offer limited efficacy coupled with debilitating side effects. New therapies that demonstrate a clinically significant improvement in efficacy (survival or time to disease progression as a surrogate to survival) and limited side effects have significant market opportunities.	MMPIs (e.g. BMS-275291, prinomastat), Taxanes: Taxol, Taxotere and generic paclitaxel. Other cytotoxics such as Gemzar, Navelbine, Camptosar, Hycamtin, 5-FU, Xeloda, Platinol and Paraplatin. Antibody therapies such as Herceptin and Rituxan. Emerging cytostatic agents such as tyrosine kinase inhibitors (e.g. Iressa, SU5416), FTIs, and other angiogenesis inhibitors (e.g. endostatin, angiostatin). The competitors will vary depending upon the cancer type(s) where ABT-518 demonstrates efficacy.
	Sales	$3,900 MM	14% global		
Ex-U.S. Market	TRX	NA		There are significant unmet needs in cancer Ex-US, where cancer is the leading cause of death in Japan and the second leading cause of death in Europe. Physicians are looking agents that demonstrate improved efficacy when used either as single agents or in combination with existing regimens.	Competitors are similar to those in the US. Government agency analyses for cost effectiveness of the therapy is important for reimbursement in some countries.
	Sales	$4,700 MM	14% global		

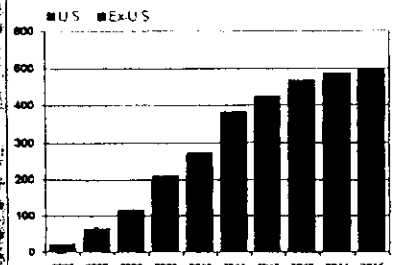
Development

Cost to NDA	DOC Est.	Thru 2000	YTD	2001 Proj.	2001 Budget	Var ($)	Var (%)	2002	2003	2004	2005	Post LRP	Total
Clinicals	$0.0	$1.6	$0.3	$2.2	$2.2	$0.0	0%	$19.0	$21.0	$19.0	$16.0	TBD	$78.8
CMC	$0.0	$1.8	$0.1	$2.2	$2.2	$0.0	0%	$8.0	$6.0	$4.0	$4.0	TBD	$26.0
Drug Safety	$0.0	$1.8	$0.6	$2.3	$2.3	$0.0	0%	$8.0	$4.0	$3.0	$2.0	TBD	$21.1
Other	$0.0	$0.4	$0.1	$0.7	$0.7	$0.0	0%	$3.0	$5.0	$3.0	$1.0	TBD	$13.1
TOTAL	$0.0	$5.6	$1.1	$7.4	$7.4	$0.0	0%	$38.0	$36.0	$29.0	$23.0	TBD	$139.0

	DOC ($MM)	LBE	Actual
Start of Tox			2Q2000
Phase I		1Q2001	
Phase II		3Q2002	
Phase III		4Q2003	
Last PV/Last Visit			
US, EU, Japan Filing		4Q2005	
US, EU, Japan Approval		2Q2006	

Commercial

Base Case Forecast ($MM)



Financial Summary	U.S. ($MM)	Int'l ($MM)
Peak Sales ($MM)	$307	$189
Peak Standard Margin ($MM)	$275	$170
Peak Standard Margin (%)	89.6%	89.9%
Pre-Tax NPV @ 12.5% (global)	$484	

Base Case Assumptions

Product Profile (Efficacy, Safety, Convenience) — Prob — Share Impact

- Safety/AE: Addition of ABT-518 to cytotoxic regimen does not add significant side effects; side effects are similar to current gold std.
- Convenience: Oral, daily therapy
- Efficacy: Initial indication: Approved for use in second line regimen in advanced patients in one medium/large cancer (e.g. breast, NSCLC, ovarian, NHL or colorectal); In combination with cytotoxic therapies demonstrates clinically significant improvement in survival or time to tumor (or disease) progression compared to current gold standard in second line therapy
- Efficacy: Second indication (in year 3): Approved as a first line therapy in advanced patients in the same tumor type as initial indication with equivalent or marginally better efficacy compared to current gold standard
- Efficacy: Third indication (in year 5): Approved as a second line therapy in a distinct tumor type, with equal or marginally better efficacy than current gold standard
- Other: US: For patients with commercial insurance, ABT-518 will be covered with a minimal co-pay (<$35). Medicare will not reimburse for ABT-518 as a self administered medication; 75% patient compliance

Commercial Profile	U.S.	Ex-U.S.
Launch Date	Q3 2006	Q1 2007
Price per Day at Launch (AWP)	$9,000.00 Similar to cancer, HIV, MS and transplant drugs	$4,500.00 Similar to cancer drugs
Sales force @ peak sales ($MM)	63	64
Promo @ peak sales ($MM)	$6	$5
COGS @launch @ peak)	90% SMM	90% SMM
Market/External/Other	Assumes 2% annual price increases	

Next Go/No-Go: End of Phase I (early 2002)

Business Rationale: With ABT-518, ABT-510 and ABT-627, Abbott can establish itself as a clear leader in angiogenesis inhibition with 3 anti-angiogenesis drugs that act by alternative mechanisms. The MMP-2 and -9 selectivity should allow for a larger therapeutic window and thus the potential for higher efficacy and lower toxicity than other MMPIs such as marimastat and prinomastat.

1 of 1

Monthly Highlights – Key Project Progress

- Study initiation visits were conducted on 2/14 and 2/15.

Next Quarter's Key Progress Markers

Key Progress Markers	Target Date
• First patient enrolled	3/12
• Preliminary results from 6-week rat hepatotoxicity study	3/31
• Pre-IND meeting with FDA	6/1
• Preliminary results from 3-month rat chronic toxicity study	6/30

Key Project Issues and Risks

Risk or Issue	Potential or Known Impact (Check all that apply and Describe Impact)	Strategy	Responsibility	Resolution Date (Planned / Actual)
Identification of FDA requirements for cytostatic agents in oncology drug development.	☐ Cost ☐ Time ☐ Profile ☑ Regulatory	Phase I IND study to Transition program to solicit FDA input.	Clinical	6/1/01
Key tox finding was hepatotoxicity in one-month rat study. *In-vitro* and *in-vivo* data indicate a potential for mechanism based drug interactions.	☐ Cost ☐ Time ☑ Profile ☑ Regulatory	The Phase I first-in-man protocol has been designed to address these issues. A 6-week tox and metabolism studies have been completed. Results are under review. A 3-month rat toxicity study is ongoing.	Toxicology/ Metabolism	7/1/01

Risk or Issue	Potential or Known Impact Check all that apply and describe impact	Strategy / Progress	Lead / Responsibility	Resolution Date Planned / Actual
As several competitors are in Phase II/III, ABT-518 product profile will need to demonstrate advantage over the other compounds (i.e., safety/efficacy)	☐ Cost ☐ Time ☑ Profile ☐ Regulatory	Ongoing analysis and comparison of competition throughout transition. ABT-518 has the potential to be the best in class compound. Pfizer (Agouron) announced 8/4/00 that they were stopping Phase III trials of prinomastat in advanced prostate and NSCLC because "primary efficacy objectives were not met". They are continuing trials in less advanced tumors, e.g., **glioma and NSCLC**, and will start trials in two additional tumor types. Efficacy was shown with marimastat in less advanced gastric cancer, but British Biotech announced on 9/27/00 that marimastat in combination with carboplatin was no better than carboplatin alone in advanced ovarian cancer. **Marimastat development was discontinued on 2/15/01.** Both the Pfizer compound and British Biotech's compound are hindered by dose-limiting joint toxicity.	Competitive Environment	
	☐ Cost ☐ Time ☐ Profile ☐ Regulatory			

Key Activities

Commercial

Activity	LBE	Actual
Market research to assess commercial potential of cancer types, both US and Ex-US....	4/2001	
Assessment of patient compliance (for revision of forecast)	3/2001	
Assessment of off-label vs. spillover use (for revision of forecasts)	3/2001	
Assessment of cancer market growth (for revision of forecasts)	4/2001	
Assist with advisory planning	4/2001	
Development of brand and generic names	Late 2001	

Formulation — Plan Date: 3/2000

Activity	Plan	Actual
Phase I Formulation	10/2000	
Phase II Formulation		
Formulation for Bio Study		
Phase III Clinical Supplies Manufactured		
NDA Lots (3) Completed		
Completion of 1 Year Stability for NDA		
Formulation Peer Review		

Drug Substance — Plan Date: 3/2000

Activity	KG	Plan	Actual	Actual Projected Cost/kg
Chem Scien (GLP)	3.0/1.7	6/2000	6/16/00	$133,300
Chem Scien (GMP)	2.0/3.8	6/2000	6/29/00	$133,300
Chem Scien	**15.0**	**6/2001**		
SPD				
SPD				
SPD				
Demo Lot				
NDA Lot #1				
NDA Lot #2				
NDA Lot #3				
Validation Lot				

Toxicology — Plan Date: 3/2000

Toxicology Activity	Planned Start	Actual Start Date	Report Completed
Gene Toxicology	5/2000		
Acute Studies	5/2000		
2-Week Monkey (non-GLP)	12/1999	12/14/99	
1-Month Rat (non-GLP screening)	12/1999	12/14/99	
1 Month Rat (GLP)	6/2000	6/27/00	
1 Month Monkey (GLP)	6/2000	6/29/00	
3 Month Rat	1/2001	1/2/01	
3 Month Mouse MTD			
SEG I and SEG II			
SEG III Rat (post natal development)			
6 Month Rat			
1 Year Monkey			
Carcinogenicity (2 yr) Rat			
Carcinogenicity (2 yr) Mouse			

HIGHLY CONFIDENTIAL
ABBT 0000346

All Clinical Studies:

Protocol Number	Phase	Study Name	Start 1st Pt. Dosed	End (Last CRF In)	Patients Target	Patients Current
M00-235	I	MD Study in cancer patients	2/28		40	
TBD	I	IND Study			20	

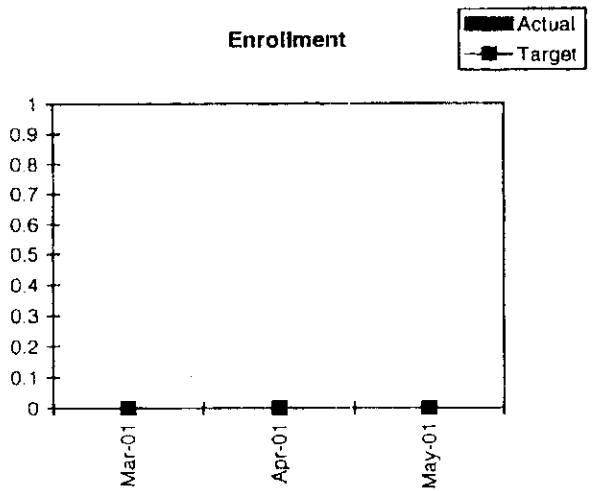
Protocol Number	Phase	Study Name	Start 1st Pt. Dosed	End (Last CRF In)	Patients Target	Patients Current

HIGHLY CONFIDENTIAL
ABBT 0000347

Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

Protocol:	**M00-235 - Phase I MD in cancer patients**	**MXX-XXX – TITLE**
Objective:	**Determine MTD and safety profile in cancer patients**	
ABT-518 Doses:	**25, 50, 100, 200, 400, 800, 1200, 1600, 2000 mg/day**	
Comparator Doses:	**N/A**	
Target Enrollment:	**40**	
Status:	**Study initiated, clinical supplies delivered**	
Major Findings:		

(Author: Double click on chart to edit)



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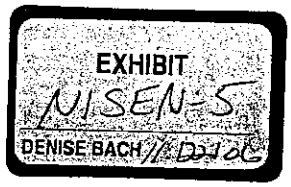


ABT-518

TRANSITION STRATEGY

(MMPI)

August 2000

ABT-518 TRANSITION STRATEGY

1. Introduction and Background

For most cancers, the level of physician satisfaction with current therapies is low given the highly toxic nature of the treatments. A new avenue being investigated is the use of "cytostatic" agents. This approach to therapy has the potential to transform cancer into a chronic disease that patients live with long-term, much like the effect protease inhibitor therapy has had on patients with HIV infection. Abbott's matrix metalloproteinase inhibitor (MMPI) program is one example of this novel therapy with the potential to alter the way cancer is treated by preventing or modifying disease progression and/or metastases.

The MMPs comprise a family of enzymes that degrade a wide range of tissue matrix protein substrates. Many solid tumors have high expression of these enzymes and this is associated with the ability of tumors to aggressively grow, invade, develop new blood vessels and metastasize. Experimental evidence suggests that the MMPs gelatinase A and gelatinase B are particularly important in tumor progression. The Discovery Project Team has therefore targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes severe joint pain and stiffness that precludes the use of high doses in clinical trials. The joint-related adverse events are believed to be related to the inhibition of other MMPs, namely MMP-1 (fibroblast collagenase).

ABT-518, a member of Abbott's biaryl ether retrohydroxamate series of inhibitors, replaced ABT-770 as the lead MMPI transition candidate. Preclinical toxicity studies with ABT-770, Abbott's first MMP inhibitor development candidate, revealed a number of adverse effects which occurred at drug exposures only several fold higher than that necessary for efficacy in animal models. The MMP selectivity and potency profile exhibited by ABT-518 distinguish it from ABT-770 and the competitor's compounds. ABT-518 possesses sub-nanomolar potency versus gelatinase B, an improvement of 200-fold over ABT-770. ABT-518 is also a substantially more selective inhibitor of the gelatinases compared to prinomastat, suggesting that it may avoid mechanism-based joint effects.

In animal tumor models, ABT-518 demonstrated anti-tumor activity equal or superior to ABT-770 and prinomastat. Inhibition of tumor growth was dose dependent in both syngeneic and xenograft models. Infusion studies with osmotic minipumps designed to determine the minimal blood levels necessary for efficacy showed that steady-state blood levels of ABT-518 ranging from 0.13 µg/ml (B-16 syngeneic melanoma) to 0.57 µg/ml (HT1080 human fibrosarcoma) resulted in biologically significant inhibition (defined as ≥ 30% inhibition of tumor growth over that of control). Comparable efficacy via the oral route was achieved with doses, given twice a day, of 3 and 10 mg/kg, respectively, in the two experimental models. These doses would be roughly 200-800 mg in humans. ABT-518 was also effective in blocking blood vessel formation in a mouse ocular model of angiogenesis.

ABT-518 gave sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailability ranged between 68 and 93% depending on formulation and species. Multiple metabolites are produced after repeated oral dosing, some reaching plasma concentrations in excess of

parent drug. Most of the metabolites result from modification of the retrohydroxamate moiety, although the relative amounts vary with gender and species. Plasma concentrations will be assessed in Phase I to determine safety margins and potential drug-drug interactions.

The preclinical safety profile exhibited by ABT-518 is more favorable than ABT-770. ABT-518 displays no significant effects in screening studies for genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. Toxicity studies in rats and monkeys (non-GLP) reveal none of the debilitation and lethality seen with ABT-770. Tissues from these animals reveal no evidence of phospholidiposis which likely reflects the reduced tissue burden of metabolites produced by ABT-518 relative to ABT-770. Plasma concentrations generated by ABT-518 in rat toxicity studies are at least 20-fold higher than that necessary to produce efficacy in animal tumor models.

Several orally bioavailable MMP inhibitors are being assessed in phase II/III clinical trials for the treatment of cancer (Table 1). Preliminary results from several trials suggest that treatment with an MMPI can cause disease stabilization. Results from Phase III studies with marimastat have been both positive (gastric cancer) and negative (pancreatic cancer and glioma) and suggest that MMP inhibitors are more likely to benefit patients at earlier stages of disease progression. A survival benefit for marimastat was seen in 101 inoperable gastric cancer patients without metastases ($p=0.033$). However, all but tanomastat report dose-limiting side-effects characterized by pain and stiffness of the joints (BMS-275291 showed Grade 1/2 joint effects). Although tanomastat is highly gelatinase selective, it exhibits only marginal to modest potency against MMP-2. The incidence of joint toxicity exhibited by marimastat, prinomastat, and BMS-275291 may negatively influence the likelihood of their ability to demonstrate efficacy in Phase II/III studies. Doses of 5, 10 and 25 mg administered BID were chosen for the Phase III trials for marimastat. These are below the dose at which joint toxicity was observed in Phase I. Seven other randomized pivotal trials with marimastat are currently ongoing in SCLC, NSCLC, breast cancer, ovarian cancer, and in glioblastoma. Pfizer announced on 8/4/00 that Phase III clinical trials of prinomastat in patients with advanced non-small cell lung cancer (NSCLC) (in combination with paclitaxel/carboplatin and with gemcitabine/cisplatin) and in advanced hormone-refractory prostate cancer patients (in combination with mitoxantrone/prednisone) have been discontinued. The reason given was that "primary efficacy objectives were not met". Both studies assessed the effect of prinomastat at doses of 5, 10, and 15 mg BID. These dose levels are below the doses at which joint pain was observed in Phase I. They are continuing trials in less advanced tumors, e.g., esophagus, melanoma, breast, glioma, and NSCLC and will start trials in two additional tumor types.

Table 1. MMP Inhibitors in Advanced Clinical Development

MMP Inhibitor Company	Development Stage	Tumor Type	Metalloproteinase Selectivity	Joint Toxicity
Marimastat British Biotech/ Schering	Phase III	NSCLC SCLC breast ovarian	Broad spectrum	yes
Prinomastat Agouron/ Pfizer	Phase III	esophagus melanoma breast glioma NSCLC* Prostate*	Moderately gelatinase selective	yes
BMS-275291 BMS/Chirosciences	Phase I/II	unknown	Broad spectrum; no TACE	yes
Tanomastat† Bayer	Phase III	SCLC NSCLC ovarian pancreatic	Highly gelatinase selective	No
ABT-518 Abbott Labs	Preclinical		Highly gelatinase Selective	TBD

* Discontinued in advanced disease. NSCLC continues in less advanced disease.

† Tanomastat (BAY12-9566) was discontinued from clinical development when an interim analysis of a study revealed increased mortality in the drug treated group. However, subsequent analysis of additional patients showed drug benefit and Bayer may resume clinical development (personal communication).

While the competition in the MMP inhibitor field is intense, no compound has yet been approved. The selectivity of ABT-518 suggests that it may be spared the dose-limiting joint toxicity observed with marimastat and prinomastat, thus expanding the range of tolerated doses and enhancing the likelihood of demonstrating clinical efficacy. ABT-518 is therefore a compelling successor to ABT-770 with the potential to demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials.

2. Transition Strategy

2.1. Objectives/attributes

The primary objective of the transition process will be to assess key attributes of ABT-518 that would justify a recommendation for full development or program discontinuation. Key desirable attributes for ABT-518 include:

- Acceptable animal toxicity profile following prolonged administration (one-month in two species).
- Favorable systemic exposure (0.1 µg/ml trough concentration) in cancer patients after oral administration not more than twice a day.
- Acceptable safety profile in cancer patients following a minimum treatment of one month.

The development activities during the transition period will be limited to two Phase I studies (a first-in-man multiple-escalating dose study ex-US and a small IND study), and the toxicology, metabolism and formulation activities needed to support Phase I activities. It is not the objective of the transition program to demonstrate proof of efficacy for this compound, as this can only be assessed during properly controlled studies.

Several Go/No Go decision points have been incorporated into the transition program, which has an overall objective of making a timely recommendation for the continuation of ABT-518 development or program discontinuation. The key Go/No-Go points are related to (1) preclinical toxicity (Sep 2000), and (2) safety and pharmacokinetics in patients from the multiple-dose study (Dec 2001). Throughout the transition, attention will be paid to the competitive environment by tracking the progress of other MMPIs in development.

2.2. Key Issues/Risk Assessment

While several issues are expected throughout the development of a new class of cancer compounds, there are some key issues and risks specific to ABT-518 to be addressed during the transition period:

2.2.1. Formulation/Drug Supplies

Nominal drug formulation work will be done during the transition stage of development. Preliminary work has shown that drug substance in a capsule, when taken with food, will provide an adequate PK profile but larger doses may be required. The lack of formulation optimization during transition will contribute to a 6-8 month gap prior to the start of Phase II.

2.2.2 Toxicology

The safety profile will need to be conducive to chronic administration in cancer patients. In screening studies, ABT-518 did not exhibit significant effects in genotoxicity, clastogenicity, cytotoxicity and ligand binding assays. In animal models, no significant CNS effects were produced by ABT-518 and the compound exhibited an improved acute cardiovascular safety profile relative to ABT-770. ABT-

518 was well tolerated in rats treated for up to four weeks and in a small number of monkeys treated for two weeks. The maximum tolerated dose in both species was greater than the highest dose tested (100 mg/kg/day). Changes produced by ABT-518 included an increase in liver weight in rats and a slight decrease in food intake in one of two monkeys tested. No joint toxicity has been observed in either rats or monkeys. However, hypertrophy seen in the growth plates of rats needs further assessment. This hypertrophy is not believed to be similar to that reported with marimastat (subphyseal fractures, fibroplasia of the musculotendinous insertion sites, and clinically evident impairment of motion) and is seen in Gel B knockout mice without resulting deformities. Based on AUC values from preclinical efficacy and safety studies, ABT-518 has a larger therapeutic window than ABT-770 in rodents. In GLP toxicity studies it will be important to assess the occurrence of phospholipidosis as this was a significant finding with ABT-770.

The relationship of tissue metabolite accumulation to long-term safety is not known but is suspected to be important. Metabolites are produced following multiple oral doses of ABT-518 in rats and monkeys, with the absolute and relative amounts being gender and species dependent. However, accumulation of metabolites in tissues of treated rats and monkeys was far less for ABT-518 than for ABT-770. Five major metabolites of ABT-518 (selected by concentration and potential reactivity) have been synthesized for analytical method development. The toxicology program will include an assessment of metabolite production and toxicity. These metabolites will also be analyzed in the Phase I study. Analysis of this many metabolites is not a trivial undertaking and it is hoped that this number can be reduced once the human metabolite profile is better understood.

2.2.3. Clinical

The objective of the clinical program during Transition is to show that the safety and pharmacokinetic profile of ABT-518 in cancer patients are similar to or better than those of the competitor compounds. A prolonged exposure period will be required to assess the potential for joint toxicity in view of the MMPI competitor experiences. A secondary objective will be to establish a dose for the Phase II program.

Four critical questions need to be answered to recommend further development:

1. Can target trough plasma concentrations of 0.1 µg/ml be achieved after oral administration of ABT-518?
2. Can ABT-518 be administered once or twice a day?
3. Can ABT-518 be administered chronically in cancer patients with an acceptable safety profile?
4. Will ABT-518 produce the joint stiffness that has been observed with other MMPIs in development?

This transition assessment will not include a single-dose study in healthy volunteers. The primary reason for a normal volunteer Phase I single-dose study is to provide single-dose pharmacokinetics (PK), thus allowing the rapid selection of a starting dose for the Phase I multiple-dose study. This was true for ABT-839 (FTI) and ABT-510 (TSP). The questions that need to be answered for ABT-518 will require multiple dosing and are unlikely to be identified in a single-dose study. In addition, the competitor MMPI, marimastat, demonstrated differences in PK between normal volunteers and

cancer patients, thus making it doubtful that the single-dose data would predict a starting dose in cancer patients.

However, if non-cancer indications are pursued, a Phase I SD/MD study in healthy volunteers may be required. Ophthalmologic indications such as macular degeneration or diabetic retinopathy would likely be topically dosed and would only require evidence of minimal systemic exposure. Indications requiring systemic exposure such as multiple sclerosis or rheumatoid arthritis would likely require additional Phase I studies in healthy volunteers.

It is known that joint toxicity is both compound-dependent and dose-dependent, and with broad spectrum MMPIs it has been seen only after four weeks of dosing or later. At lower doses it took more than eight weeks for the toxicity to be seen. While reports of joint toxicity during the initial portion (28 days) of the study are unlikely, this dose-limiting toxicity will be assessed during the extension portion of the study.

The planned multiple-dose study (and its extension) will establish ABT-518 pharmacokinetics in patients, and more importantly will assess the safety profile following a minimum of 28 days administration. The duration of the study and it's extension will be sufficient to project the safety risks for chronic use of this class of cytostatic agent. The study objectives will be to:

- Identify the dose that will provide acceptable systemic exposure after oral administration (plasma trough concentrations of 0.1 μg/ml).
- Assess acute and multiple-dose safety.
- Identify potential doses for the Phase II program.

3. Transition Program

In order to achieve the above objectives and assess the ABT-518 specific attributes and issues, the Transition Team will carry out the activities described below:

3.1 Bulk Drug Synthesis

- 100 grams of non-GMP drug was delivered 12/99 by Chemical Sciences for selection of ABT-518 as a candidate.
- 1.7 kilograms of non-GMP material was delivered 6/00 for the one-month animal toxicity studies.
- 3.8 kilograms of GMP material was delivered 6/00 for the Phase I multiple-dose study.
- 10 kilograms of GMP material will be delivered 3Q01 to complete the Phase I trial with extensions and initiate Phase II preparation. This campaign might be larger depending on Chemical Sciences process initiatives.

3.2 Formulation Activities

- Available "drug in a capsule" data have demonstrated >63% bioavailability in fed dogs. Based on these data, the Transition Team will proceed into Phase I with drug substance in a capsule

administered with food. Capsule strengths will be 25 mg and 200 mg to provide dosing flexibility with minimal patient inconvenience.

- No further formulation work is planned during the transition phase beyond preliminary experiments of limited scope. If a Go decision is made at the end of Phase I, a minimum of 9 months (3-4 months for bulk drug delivery and 6-8 months for PARD) will be needed to support Phase II studies. These activities will depend on the PK and safety results seen in the Phase I study and may be accelerated at risk based on preliminary results.

3.3. Toxicology Program

The toxicology program has been designed to provide the data required to support the Phase I clinical program. The Toxicology plan includes the following studies:

- Acute studies in rodents
- 1-month repeat dose studies in rats and monkeys
- Genotoxicity evaluation for mutagenic and clastogenic potential

One-month toxicology studies were started 6/00 with results available 9/00 to support the first-in-man multiple-dose study. On the basis of these studies several key safety determinations will be made: 1) identification of target organ toxicities, 2) determination of reversibility of tissue changes with drug discontinuation, 3) characterization of the contribution metabolites have on toxicity, and 4) recommendation for acceptable starting dose for human studies.

Challenges include: 1) measurement of five primary metabolites in plasma (and possibly tissues) as well as evaluation of their genotoxicity potential in a selection of mutagenicity and clastogenicity assays, and 2) decrease in plasma drug concentrations with repeated dosing may be a limiting factor for attaining target organ toxicity. Although autoinduction of ABT-518 metabolism is a likely cause, other possibilities exist, including formulation limitations and changes in absorption. These issues will be further characterized in the one-month studies.

3.4. Metabolism Program

Metabolism studies will continue throughout the transition period. Specifically, ongoing studies will focus on confirming the structure of circulating metabolites identified by co-chromatography and other, as yet unidentified, circulating plasma and tissue metabolites that were present in the 1-month non-GLP toxicology studies. Pending the successful synthesis of radiolabeled ABT-518, a mass balance and excretion study will be conducted to confirm quantitative recovery of dosed radioactivity and to determine the ultimate elimination products of ABT-518 *in vivo*. Basic *in vitro* studies will also be undertaken with ABT-518 and available metabolite standards to explain the metabolic disposition of ABT-518 in toxicological models (rat and/or monkey). Similar *in vitro* experiments in human models will be conducted in an attempt to describe likely metabolic disposition of ABT-518 and its metabolites in humans. These studies will be available prior to the initiation of the Phase I multiple-dose study.

3.5 Regulatory

The Phase I multiple-dose study will be conducted ex-US without an IND. The Phase II program is planned to be conducted under a US IND. To facilitate initiation of the Phase II program, a small (14 patients) Phase I study will be submitted to the FDA to open the US IND. The IND will be opened 2Q01, prior to completion of the multiple-dose study and will facilitate the Phase II program by early identification of issues/requirements raised by the FDA. Opening the IND in 2001 could potentially reduce the development gap between Phase I and Phase II.

An additional benefit of this approach would be to establish a good working relationship with the FDA Oncology Division.

3.6. Phase I Multiple-Dose Study in Cancer Patients

The goals of the multiple-dose study in cancer patients are to determine the maximum tolerated dose (MTD), and evaluate the safety and pharmacokinetics of escalating doses of ABT-518. In the study 6-10 cohorts of cancer patients will be treated with a course of ABT-518, with a course being defined as 28 days of treatment. Each cohort will consist of a minimum of 3 patients diagnosed with refractory cancer. The starting dose for the 1st cohort will be determined by results of the one-month rat and monkey toxicity studies. Subsequent cohorts will be escalated by 25% - 100% dependent on the PK profile (parent and metabolites) and observed toxicity. Escalation will discontinue once dose-limiting toxicity occurs in 2/3 of patients in a cohort. This dose will become the MTD. An additional 6 patients will be exposed to ABT-518 at the previous dose level to acquire additional safety data.

Patients who wish to continue treatment with ABT-518 will be enrolled into an extension study, where they will be treated until dose limiting toxicities are reported or disease progression occurs.

3.6.1. Primary Objectives of the Study:

- Identification of an MTD.
- Assessment of the pharmacokinetics of the parent compound and achievement of a trough plasma concentration of 0.1 μg/ml.
- Assess clinical dosing frequency of QD and BID.
- Assess the safety profile after multiple doses in cancer patients with particular attention to joint toxicity.
- Recommend a Phase II dose(s).

3.6.2. Secondary Objectives:

- Evaluate the relationship of MTD to biologically significant inhibition.
- Assess a biomarker of activity in relation to drug exposure.
- Evaluate the metabolite profile in patients.

3.6.3. Decisions Based on Multiple-Dose Study Results

At the completion of the Phase I multiple-dose study a Go/No Go decision will be made based on the safety and pharmacokinetic data. If targeted trough concentrations (0.1 µg/ml) after oral dosing with ABT-518 cannot be achieved, or if either an excessive dose (greater than 2 grams) or dosing frequency of more than BID is required, a recommendation on program discontinuation will be made. If results reveal considerable toxicity during the chronic administration of the targeted therapeutic dose, continued development of ABT-518 will be considered on the basis of potential benefit/risk ratio and the status of competition at that time. Evidence of joint toxicity reported during the study will be evaluated against what is known about the competitors' MMPIs.

4. Backup Strategy

From an intellectual property perspective, the MMP inhibitors field is quite mature. Over the past 10 to 15 years a steady stream of patent applications covering a range of structural classes have been published. Novel compositions of matter, particularly within the succinyl and biaryl hydroxamate classes, are now scarce. The biaryl ether retrohydroxamate class of MMP inhibitors provides Abbott with a patent niche within this very crowded field. The attributes and liabilities of this class have been fully explored by the Project Team; more than 390 retrohydroxamates were synthesized and extensively characterized over a 2-year period. While exceptions are always possible, it seems unlikely that the properties of ABT-518 can be vastly improved upon through further SAR within this series. Backup compounds to ABT-518 could be readily identified, yet they are apt to possess very similar properties. The opportunity to pursue other lead structures, generated through NMR screening or by other means, remains as a viable option, yet these endeavors must be viewed relative to other activities within Cancer Research. At this time the Project Team is applying no further effort to the discovery of novel MMP inhibitors.

5. Post Transition

The objective of the transition process is to conduct only those activities that are necessary to reach a Go/No Go decision for full development, thus minimizing the cost of early development. As such, once a Go decision is made following the Phase I program, there will be a delay of 6-8 months before initiating Phase II. This would be the time required to complete the necessary bulk drug synthesis, formulation activities, and regulatory preparation in order to proceed with the Phase II program. This gap could be minimized by resuming critical activities in support of Phase II prior to completion of the Phase I studies.

6. Timeline/Milestones

	Initiation	Completion
• Bulk Drug Delivery (1.7 kg non-GMP)	Mar 00	Jun 00
• Toxicology	Jun 00	Oct 00
- One-month rat	Jun 00	Sep 00
- One-month monkey	Jun 00	Sep 00
- Genotoxicity & acute studies	Jun 00	Aug 00
• **Go/No Go Decision Preclinical Safety**	**Sep 00**	**Sep 00**
• Bulk Drug Delivery (3.8 kg GMP)	May 00	Jun 00
• Formulation Development & Clinical Supplies	Jun 00	Sep 01
• Phase I MD (28 days)	Nov 00	Dec 01
• Pre-IND Meeting with FDA	Feb 01	Feb 01
• Submit US IND	Apr/01	Apr/01
• Initiate US Phase I	Jun 01	Jun 01
• Bulk Drug delivery (10.0 kg GMP)	Jun 01	Aug 01
• **Go/No Go Phase II**	**Dec 01**	**Dec 01**
• **Initiate Phase II**	**Apr 02**	**Apr 02**

7. Transition Costs ($MM)

	2000	2001
Clinical Program *	1.8	2.2
CMC (PARD, Chemical Sciences, Discovery)	2.3	2.3
Drug Safety	1.8	2.0
Other support costs †	0.1	0.2
Total	**6.0**	**6.7**

* Clinical Program = Grants, Data Mgt/STATS, Venture Management
† Other Support Costs = Regulatory Affairs, RQA, Medical Services

CONFIDENTIAL

ABT - 518

Descriptive Memorandum

February 2001

Abbott Laboratories

MMPI

Overview

Abbott's Matrix Metalloproteinase Inhibitor (MMPI) program represents a novel therapeutic class, with the potential to alter the way that cancer is treated by preventing or modifying disease progression and/or metastases. This more "chronic" approach to therapy has the potential to transform cancer into a disease that patients live with, much like the effect of HIV protease inhibitors on patients with AIDS. It also has the potential to expand the cancer market significantly by increasing the average length of treatment and expanding the pool of patients eligible to receive therapy.

The MMPs comprise a family of enzymes that degrade a wide range of matrix protein substrates. High expression of these enzymes occurs in cancer and is associated with the ability of tumors to grow, invade, develop new blood vessels and metastasize.

MMP inhibitors (MMPIs) may suppress the progression of tumors by several mechanisms:

- Suppress invasion/metastasis by blocking the membrane traversal and access to blood/lymphatic vessels
- Blocking the remodeling of extra-cellular matrix in the vicinity of primary tumors to prevent stroma-bound growth factors from stimulating tumor growth
- Blocking angiogenesis by preventing the proliferation and migration of endothelial cells and neovascularization of tumor.

Experimental evidence suggests that gelatinase A and gelatinase B are particularly important in tumor progression, consequently the project team has targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes a dose-limiting side-effect characterized by severe joint pain and stiffness. Since these joint effects may be mediated by inhibition of other MMPs like fibroblast collagenase, highly gelatinase selective agents may be efficacious without producing dose-limiting side effects.

The MMP selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds. ABT-518 possesses sub-nanomolar inhibition potencies versus both gelatinase A and gelatinase B and is substantially more selective for the inhibition of the gelatinases over fibroblast collagenase than marimastat and prinomastat. Despite its high selectivity, ABT-518 demonstrates antitumor activity equal or superior to prinomastat. Inhibition of tumor growth is dose dependent in both syngeneic and xenograft models. ABT-518 is also effective in blocking vessel formation in a mouse model of angiogenesis. ABT-518 is a stable crystalline solid which can be synthesized in six steps (25% overall yield) from commercial starting material.

ABT-518 gives rise to sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailabilities range between 68 and 93% depending on formulation and species. Several metabolites are produced after repeated oral dosing of ABT-518, although their relative amounts varies with gender and species.

ABT-518 displays no meaningful effects in genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. ABT-518 produces no significant toxic effects in rats treated with 100 mg/kg/day over 28 days. Plasma concentrations generated by ABT-518 in these studies are at least 20-fold higher than those necessary to produce efficacy in cancer animal models. ABT-518 is therefore a compelling development candidate with the potential to

demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials. Phase 1 clinical trials in cancer patients began March 2001.

The market

Currently, cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market.

Global Sales by Market Segment ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Sales by Region ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the MMPI will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, MMPIs will probably be adopted initially as add-on the current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast

Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL

Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian

Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas

Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

Compounds in Development

The MMP inhibitor field is competitive. More than 30 firms have filed patents claiming small molecule MMP inhibitors over the past 5 years, and several companies have compounds in advanced clinical development. Abbott's compound may be 3rd or 4th to market and will have to demonstrate a competitive advantage to gain the share necessary to support the clinical development of this compound. Companies with compounds in advanced clinical development for the treatment of cancer include Agouron/Warner Lambert/Pfizer, British Biotechnology/Schering Plough and BMS and are listed below. Other companies are targeting this mechanism for arthritis.

MMPIs in Clinical Development for Cancer

Compound	Company	Comments	Phase
Marimistat	BritishBiotechnology/ Schering Plough	Broad spectrum, dose limiting toxicity. Activity seen in gastric cancer, but negative results in pancreatic.	III
Prinomastat	Agouron/ Warner Lambert/ Pfizer	Moderate gelatinase selectivity, dose limiting toxicity. May be dosing sub-optimally to avoid toxicity. Efficacy data not available.	III
BMS 275291	BMS	Broad spectrum, joint effects seen in Phase I studies.	II

Bayer recently dropped development of BAY 12-9566 due to concerns about potential toxicity. Recent results from a study with marimistat in pancreatic cancer, where adding marimistat to Gemzar resulted in no survival advantage, has led to speculation that MMPIs may be more applicable in less aggressive cancer types or earlier stages of the disease. Alternatively, it could be a reflection of the inability to examine higher doses of marimastat due to joint effects.

The joint effects produced by the compounds listed above almost certainly preclude their long-term use, limit compliance and reduce optimal efficacy. Any MMP inhibitor that lacks these side effects will possess a substantial competitive advantage. The musculoskeletal effect produced by marimastat and prinomastat in cancer patients is typically described as arthralgia, myalgia and tendinitis, which occurs predominately in the upper limbs. While mild cases respond to analgesics, interrupting therapy for a period of approximately 2 weeks is necessary when the condition is less well tolerated.

Although Abbott's timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott's compound is superior to those currently in clinical trials, and has the potential to be best in class.

Product profile

The objective of a product profile at this time in the product's development is to provide a target for the types of attributes that will be required to be commercially successful. This profile is based on market research with oncologists and consultation with opinion leaders. This profile will continue to be refined as more is known about this product's profile, development of competitive products and the market continues to evolve.

	Base	Optimal
Efficacy	ABT-518, alone or in combination with best therapy, provides at least one of	Provides more than one of the efficacy benefits outlined.

	the following benefits in at least one solid tumor type: • Increased survival • Tumor regression • Improved quality of life • Increased time to tumor/disease progression	
Competitive advantage	ABT-518 will need to demonstrate a clinically significant advantage in efficacy (see parameters above) or additive synergistic activity with current/competitive agents or clinically significant advantage in side-effect profile relative to other MMPI agents.	Same
Administration	Convenient administration relative to competitive agents.	Same plus reimbursement in US market.
COGS	A finished cost of goods that is consistent with at least an 80% standard manufacturing margin.	A finished cost of goods that is consistent with at least a 90% standard manufacturing margin.

Marketing overview

Product Usage: Physicians have indicated that they would use MMPIs initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. The MMPI was regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy.

Product Benefits/Efficacy: Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. The MMPI mechanism has more recently been implicated as having an even more active role in cancer pathogenesis, from preventing primary tumor growth to anti-angiogenic properties. Positive results from competitive agents, such as marimistat in gastric cancer, provides proof of principle for this mechanism.

Side Effects: The proposed safety profile of MMPIs (excluding joint toxicity) may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, MMPIs may *have* to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance. As the 3rd or 4th MMPI to market, SE hurdles will be even higher for this compound. As a critical Go/No Go decision point, the joint toxicity of this compound will be evaluated in an expanded Phase I multi-dose study.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are acknowledged by physicians and patients as being more convenient to the patient. Chronic oral dosing may also reduce overall costs, as infusion support products and personnel would not be required, enhancing pharmacoeconomic evidence.

COGS: Initial estimates on finished cost of drug suggest that drug costs will not be significant for this compound

Off-label use: Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

Competition: As the 3rd or 4th MMPI to market, Abbott's compound will need to demonstrate a meaningful clinical advantage over compounds that are in more advanced development. Strict Go/No Go criteria will determine if the MMPI can meet these hurdles. If they cannot be met, the compound will not move forward.

Development/Regulatory: With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several MMPIs in late stage development, Abbott can learn from their experience.

Other Approaches: Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

Pricing: The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. However, as an oral therapy in the US market, there may be additional downward price pressure for this agent. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

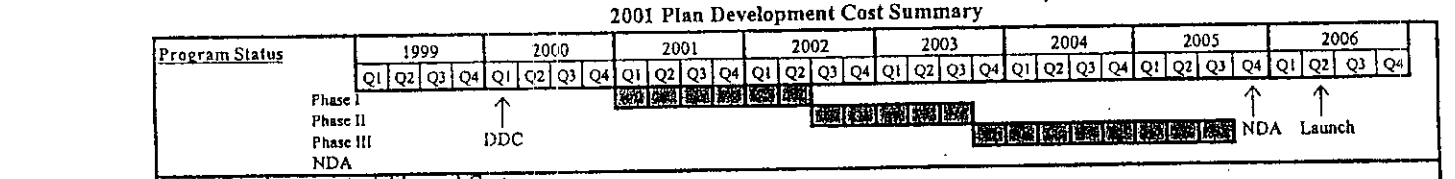
Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are preferred by physicians and patients because of the convenience to the patient. However, this form may not be the best choice for some people who already have certain digestive system symptoms (vomiting, diarrhea, or severe nausea), cannot swallow liquids or pills, or cannot remember when or how many pills to take. Additionally, in the US market there are several unique factors that currently do not favor oral therapies. Novel oral therapies are not currently reimbursed by Medicare, a significant payer for the oncology patient population. Also, 40-60% of a community oncologist's income is generated through the administration of IV drugs. An oral therapy would not be a source of revenue to the physician.

Clinical Studies

Clinical studies across a wide range of solid tumors will be initiated, including but not limited to breast cancer, non small cell lung cancer, ovarian cancer, pancreatic cancer, etc...

Final indications pursued will depend from the results of the phase II studies.

MMPI (ABT-518)
2001 Plan Development Cost Summary

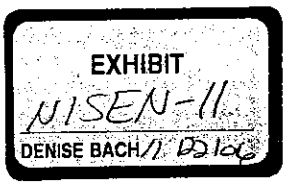


Major Development Activities and Costs	Total Patients	Enrolled as of 8/00	Start	End	2000 AGU Cost	2001 Plan Cost
Clinical Program						
Multiple Dose in Cancer Patients	40	...	1Q/01	1Q/02	$300	$769
IND Study	14	...	3Q/01	1Q/02	...	$500
Other Studies / EVR					...	$108
Phase-I Center / PK					$70	$65
Venture Management					$778	$754
Data Management/Statistics					$57	$118
					$1,205	$2,314

Chemistry, Manufacturing, and Controls (CMC)	2000 AGU	2001 Plan
Formulation / Analytical	$546	$1,031

Drug Safety Support	2000 AGU	2001 Plan
Ongoing Drug Safety support	$1,681	$2,125

Other Support Costs		
Discovery	$1,447	$1,348
Medical Affairs	$5	$20
Regulatory Affairs / Research Quality Assurance	$26	$39
Other / In-licensing Fees	$90	$123
Total Program	$5,000	$7,000



Abbott Portfolio Review

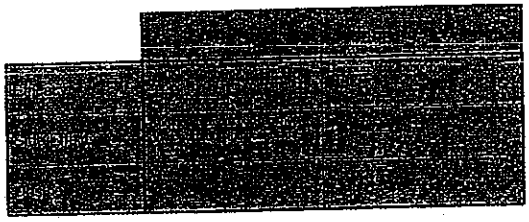
March 7-9, 2001

- Project: ABT-518
- Compound: Matrix Metalloproteinase Inhibitor
- Presenter: Perry Nisen
- Project Team Members

A. Nabulsi (VH), T. Janus (MD), D. D'Amico (CPM)

ABT-518

- Target indication: Solid tumors
- Targeted unmet medical need: Cancer
- Target product profile vs. current gold standard:

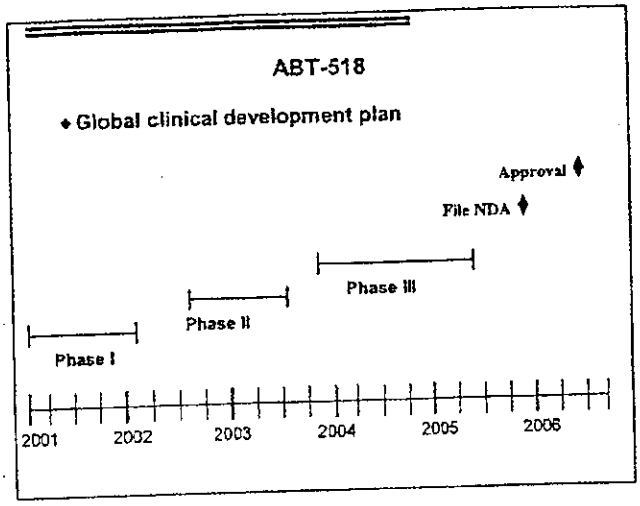


ABT-518

- Key pre-clinical findings:
  - Pharmacology
    - Potent and highly selective (gel-A and gel-B) MMP inhibitor
    - Anti-tumor activity seen in numerous murine cancer models
    - Inhibition of tumor growth is dose dependent
    - Blocks vessel formation in a mouse model of angiogenesis
  - Pharmacokinetics / Metabolism in animals
    - Sustained plasma concentrations following single-dose in monkeys
    - Oral bioavailability between 68 and 93% in animals
    - Multiple metabolites are produced after repeat dosing in rats and dogs
  - Toxicology
    - No meaningful effects in genotoxicity, cytotoxicity or ligand binding assays
    - No remarkable cardiovascular effects in dogs
    - Steatosis seen in high-dose rats two weeks after drug stopped

ABT-518

- Chemistry and Manufacturing
  - Drug substance
    - Six steps from commercial starting materials
    - 3-month turnaround time to manufacture
    - Manufactured at Abbott
  - Drug product
    - Neat drug in a capsule (25 and 200 mg) for Phase I
    - Hand-fill or semi-automation at a third party manufacturing facility (Phase II)
    - Formulation development work will begin post Phase II Go/No Go decision



ABT-518

- Clinical development budget

Phase	Funding ($MM)
Pre-Clinical	5
Phase I	12
Phase II	47
Phase III	78

ABT-518

- **Phase I study:**

  Multiple-dose study in patients with advanced cancer

  - Objectives
    - Establish safety profile
    - Determine the maximum tolerated dose (MTD)
    - Assess PK
    - Determine Phase II dose
  - Design
    - 28 days + extension
    - Single-dose of drug administered on Day 1; resume dosing (daily) on Day 4
    - Approximately 40 patients; 3 patients per dose
      - Add 6 or more patients at MTD to collect additional safety information
    - Doses: 25, 50, 100, 200, 400, 800, 1200, 1600, 2000 mg/day

ABT-518

- **Phase I plan:**

  IND Study

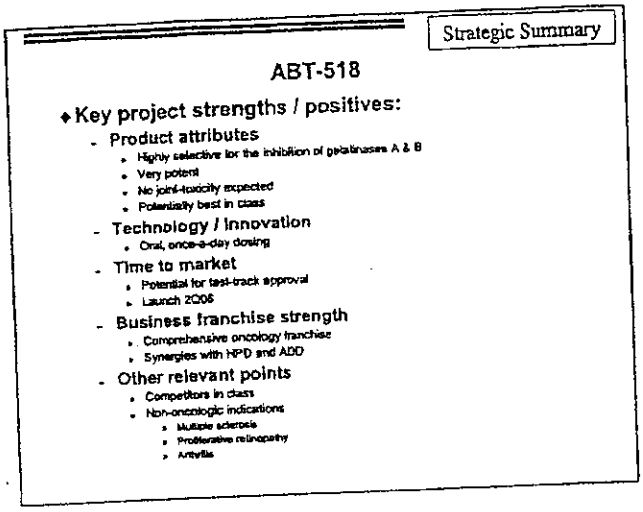
  - Objectives
    - PD-guided Phase II dose selection
    - Long-term safety
  - Design
    - Multiple dose escalation study
    - Assess MMP activity in accessible tumors
      - Melanoma
      - Head and Neck Cancer
    - Approximately 20 patients

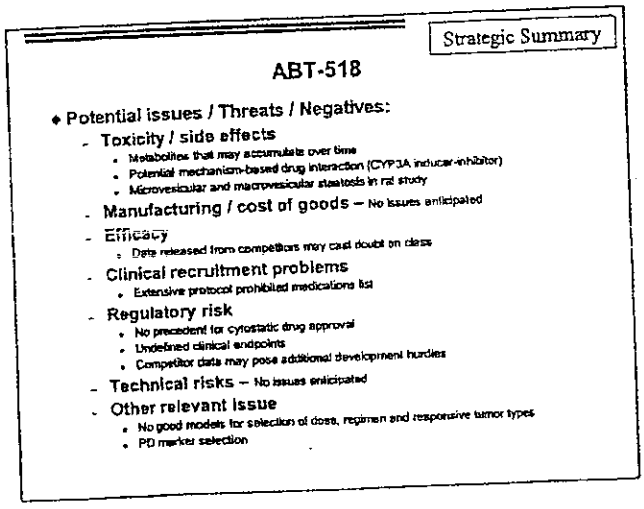
ABT-518

- Phase II development plans:
  - 3 Studies
    - 3 Tumor types as defined by Phase I and animal efficacy
    - 150 patients per study
  - Dose finding
  - Assess safety issues identified in Phase I
  - Thirteen month duration

ABT-518

- Phase III plan:
  - Demonstrate improvement in survival or TTP in combination with cytotoxic therapies





Strategic Summary

ABT-518

- **Key decisions:**
  - Important upcoming decisions
    - Transition team Go/No Go Phase II - 12/01
  - Proposed budget (2001, and all years to launch)

Year	R&D per year ($MM)
2001	7
2002	38
2003	56
2004	29
2005	23
2006	8

Strategic Summary

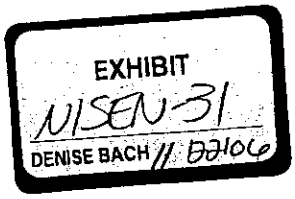
ABT-518

- **Key decisions:**
  - Evaluate safety at multiple doses and dose regimens
  - Dose and regimen selection for Phase II
  - Tumor type selection for Phase II
  - Clinical trial design to demonstrate efficacy

Strategic Summary

ABT-518

- **Proposed action plans**
  - **Manufacturing**
    - Initiate formulation work post Phase II Go/No Go
  - **Nonclinical**
    - Additional toxicology and metabolism studies are underway to explore the CYP3A and steatosis issues
  - **Clinical**
    - Measure metabolites in Phase I
    - Assess bioactivity via PD markers in Phase I
    - Hold a Pre-IND meeting with the FDA to discuss endpoints
  - **Contingency plan**
    - Pursue alternative indications
      - Multiple sclerosis
      - Proliferative retinopathy
      - Arthritis



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August 10, 2001

To: Perry Nisen D48J, AP30

Re: **ABT-518**

Below please find commentary on the results from the ABT-518 clinical trial, the status of the MMPI competition and an opinion on a path forward for Abbott's MMP inhibitor program. To summarize, the lack of clinical efficacy of competitors' compounds likely relates to their inability to maintain plasma concentrations above target levels, due to dose-limiting musculoskeletal effects. Based on the clinical data generated thus far, the exposure and toxicity profile of ABT-518 provides evidence that it may overcome these drawbacks. Completion of Phase I studies in cancer patients is recommended.

I. ABT-518 Clinical Results - Pharmacokinetics

Despite the limited number of patients analyzed thus far, the pharmacokinetics produced by ABT-518 appears to have met our objectives. The estimated plasma half-life (20 hours) is consistent with once daily dosing and the Cmax /Cmin ratio (1.8 to 6) [1, 2] is far smaller than that produced by prinomastat (30 to 55).[3] The mean trough concentration for the two patients given a 50 mg dose of ABT-518 was 380 ng/mL (760 nM), a value within the range of our original target concentrations (see Section IV below). One concern based on preclinical animal studies was the possibility of ABT-518 inducing its own metabolism. While there is a trend towards lower AUCs on Day 22 versus Day 1, significant metabolic induction does not appear to be an issue for the 25 mg and 50 mg doses of ABT-518. It would be interesting to match ABT-518 exposure to patient gender, given the substantial differences that were observed in male and female rats preclinically.[4]

Based on the pharmacokinetic profile of one patient given a 25 mg dose over 22 days, metabolite exposure was low relative to parent drug, the highest metabolite to parent ratio being produced by the amine metabolite.[5] This is consistent with preclinical studies in rats and monkeys wherein "pharmacologic" doses of ABT-518 resulted in low metabolite to parent ratios.[6] It is important to recognize, however, that the analysis is not complete without assessment of the aryl sulfonic acid, a metabolite that was identified after development of the clinical assay.

II. ABT-518 Clinical Results – Toxicity Profile

The toxicity profile produced by ABT-518 is perhaps the single most important factor in deciding whether further development is justified. A summary of the SAEs observed during this study has been distributed however a determination as to whether these events were drug related is not yet available. Clearly, a decision on whether to propose additional studies with ABT-518 is contingent on these results.

Since abandoning the broad spectrum MMP inhibitor approach in 1997, we have argued that Abbott's gelatinase-selective MMP inhibitors would differentiate themselves from the competition by avoiding the joint toxicity "ceiling" seen with marimastat and prinomastat. Joint pain and tenderness was observed in approximately 33% of patients treated with a 10 mg dose of marimastat twice daily over 5 months.[7] Musculoskeletal effects significant enough to cause dose modification or discontinuation of treatment was

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seen in 27% of patients given a 25 mg dose of prinomastat twice daily over a 4 to 8 week period.[3] It is therefore quite encouraging that arthralgia & myalgia was not reported (as far we know) in any of the patients dosed with ABT-518 for as long as two months. While the number of patients is clearly too small to draw definitive conclusions, the lack of joint effects seen with ABT-518 is certainly suggestive that ABT-518 may indeed avoid the pitfalls of marimastat and prinomastat.

III. Competition

Since it appears that the development of ABT-518 is largely predicated on the status of competitors' compounds, a review of the latest news on the leading inhibitors is provided below.

Marimastat
2001 ASCO abstracts:[8, 9]

- Marimastat (10 mg, po, bid) did not enhance overall survival or progression free survival of SCLC patients following first-line therapy. A slightly smaller study involving patients with glioblastoma multiforme produced the same result.
- In the SCLC trial, a significant percentage of the patients required either dose modification (20%) or withdrew from treatment (18%) due to musculoskeletal effects.

Independent of the negative results reported for marimastat at the 2001 ASCO meeting its development status is a bit cryptic. The IDdb investigational drugs database indicates that one study of marimastat in patients with resected pancreatic cancer is being continued since interim analysis did not meet the stopping criteria. Surprisingly, little information is available on the follow-up to study 145 involving marimastat in gastric cancer patients. One report mentioned that "long-term data (from study 145) demonstrated that patients treated with marimastat continue to show survival benefit compared with those receiving placebo", yet this study does not show up on the BBT website nor can it be found in clinical trial databases.[10] To complicate matters further, the latest issue of the *Journal of Clinical Oncology* includes a paper indicating that marimastat is as effective as gemcitabine in treating patients with unresectable pancreatic cancer, but is associated with a lower incidence of grade 3 & 4 toxicities.[11] According to BBT executives, the future direction of marimastat development is the "subject of ongoing discussion with Schering-Plough and with external experts".[10]

Prinomastat
2001 ACSO abstracts:[3, 12, 13]

- Phase III studies of prinomastat (in combination with paclitaxel and carboplatin) in NSCLC patients revealed no benefit in terms of overall survival; this was also true for a Phase III combination study in patients with metastatic hormone refractory prostate cancer.
- In a Phase II study of prinomastat in patients with progressive breast cancer, joint toxicity required treatment rest or discontinuation in 21% of patients given a 5 mg dose between 8 and 24 weeks and 27% of patients given a 25 mg dose between weeks 4 and 8.
- When asked what the future holds for prinomastat, ***each*** of the presenters responded with "assessment in earlier stage disease", yet ***none*** of the presenters were willing to define the nature of these trials; a go/no go decision on prinomastat will be made following these studies.

Pfizer discontinued the Phase III studies mentioned above in August of 2000 due to failure to meet primary efficacy objectives. However, patients having earlier stage disease in a second ongoing NSCLC trial are

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apparently continuing treatment. The IDdb database indicates that prinomastat is being assessed in four Phase II trials with two additional trials planned.[14] The design of these trials and whether they are all being conducted is not known.

BMS 275291

2001 ASCO abstracts:[15 – 17]

- Phase I studies of BMS 275291 in healthy volunteers and cancer patients indicated that it produces no joint effects different than placebo; BMS scientists continue to believe that this reflects the compound's lack of sheddase activity.
- Due to the presence of the free sulfhydryl group, BMS 275291 forms disulfides with other thiol-containing compounds. Pharmacokinetic analysis of BMS 275291 therefore includes "free" (unchanged parent) and "total" (parent measured after disulfide reduction). Unchanged parent is believed to be the pharmacologically active form.
- The stereocenter adjacent to the thiol group of BMS 275291 is partially racemized to the 60-fold less active (R,S,S) diastereomer in humans. This is apparently a recent finding and may explain why some of the trough concentrations reported in the ACSO abstract differ from those presented at the meeting (see, for example, abstract #301 (Gupta, E. et al.): trough concentrations produced by the 1,200 mg dose at steady-state: abstract = 398-567 ng/mL; poster = 158 ng/mL).
- While Cmax and AUC values of unchanged BMS 275291 increased in relation to dose from 600 to 1,800 mg, abstract #301 reports "no further increase in exposure between the 1,800 and 2,400 mg dose".
- The Phase II/III recommended dose is 1,200 mg, once daily. This dose produces unchanged parent trough concentrations of 158 ng/mL (Gupta study) which exceeds the gelatinase A/B IC_{50}'s for BMS 275291 (20 and 14 ng/mL), but exceeds the IC_{50} value only for gelatinase B (gelatinase A IC_{50}: 261 ng/mL; gelatinase B IC_{50}: 119 ng/mL).
- Dermal wound angiogenesis (measured following punch biopsy) was delayed in patients treated with BMS 275291, yet this response was not dose-dependent, consequently their Phase II/III dose (1,200 mg) was chosen based on plasma exposure.
- Phase II studies include NSCLC patients in combination with paclitaxel/carboplatin as well as Kaposi's sarcoma patients.

The BMS data presented thus far suggests that inhibition of MMP1 does not mediate joint toxicity. Whether TACE is the culprit is not known; it remains possible that MMPI-induced joint effects are due to inhibition of some unknown metalloproteinase. Regardless, several observations suggest that BMS 275291 may have more ills than originally thought. First, there are no published reports describing its preclinical efficacy in cancer animal models. Given that the compound has been described at a number of major meetings, this may indicate that its efficacy in animal models doesn't compare favorably to the other MMP inhibitors being developed. BMS 275291 is not highly protein bound (ca. 60%),[15] yet its pharmacokinetics are confounded by disulfide formation as well as racemization to a less active diastereomer. While the lack of joint effects clearly provides BMS 275291 with an advantage over marimastat & prinomastat, the report that doses higher than 1,800 mg did not cause an increase in plasma concentrations suggests that this compound may also suffer from a dose "ceiling", albeit for reasons different than its predecessors.[15]

BAY 12-9566

2001 ASCO abstracts:[18]

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- Follow-up to study of BAY 12-9566 in patients with ovarian cancer which was closed (based on data from pancreatic/SCLC patients) after enrolling 243 patients. Results from this study indicate that BAY 12-9566 (800 mg, po, bid) was neither beneficial nor detrimental. This provides evidence that MMP inhibition is not inherently harmful to cancer patients.

RS-130830

Roche's "selective" hydroxamate-bearing MMP inhibitor (RS-130830) was apparently discontinued due to musculoskeletal side effects.[19] It's MMP inhibition profile is similar to ABT-518, although TACE data for RS-130830 has not been reported.

IV. Why They Failed & Why We Might Not

A commonly cited explanation for the failure of marimastat, prinomastat and BAY 12-9566 in Phase III clinical studies has been the idea that MMPs do not play a significant role in mediating the progression of advanced stage solid tumors. Results from the Phase II studies being conducted with prinomastat in earlier stage disease will hopefully shed light on whether this is indeed the case. Given the likelihood that objective responses will not be observed in these studies, the establishment of a pharmacodynamic marker of MMP inhibition is very important for our MMPI development program (see Section V). Measurement of MMP proteolytic activity in human tumors would also be useful in identifying tumors types likely to respond to MMP inhibitors. To date the choice of which tumors to target for Phase III trials has been based largely on MMP expression, a read-out that is only an indirect measure of MMP function. This is a consequence of MMP proteolytic activity being regulated at several post-transcriptional steps including proenzyme activation and endogenous inhibitor (TIMP) complexation.

Independent of whether MMP inhibitors will perform better in earlier versus later stage cancers, there is evidence to suggest that marimastat, prinomastat and even BMS 275291 are inappropriate tools to answer this question in the clinic. Figure 1 illustrates why. This figure provides a comparison of target plasma trough concentrations based on preclinical efficacy studies, with trough concentrations achieved in cancer patients (you'll recall that this analysis was presented at the March 2000 DDC meeting and again at more than one MMPI Transition Team meeting). Based on our own studies and those in the MMPI literature, continuous exposure to MMP inhibitors is necessary for maximal efficacy in cancer animal models, thus the emphasis on maximizing *trough* concentrations. We have argued that the gelatinases are the most important MMPs for mediating tumor progression, consequently the mean IC_{50} value for gelatinase A and gelatinase B is used in Figure 1 (using either value alone produces that same conclusion). Taking prinomastat as an example, its "plasma binding-corrected" (PBCed) IC_{50} value in mouse plasma can be determined by multiplying its mean gel A/B IC_{50} value (0.048 nM) by a factor representing its "free fraction" which is based on its mouse plasma protein binding value determined *in vitro*. Prinomastat's protein binding in mouse plasma was determined to be 81.6% (0.816) therefore its free fraction is 0.184 (1 minus 0.816) and its PBCed gel A/B IC_{50} value in mouse plasma is 0.26 nM (1 divided by 0.184 times 0.048 nM). To determine the trough plasma concentration of prinomastat associated with preclinical efficacy, it was administered by osmotic minipumps in the B16 subcutaneous tumor growth model. Efficacy was observed at a continuous (trough) plasma concentration of 57 nM. For prinomastat there is therefore a 218-fold shift between the mouse PBCed gel A/B IC_{50} value and the plasma concentration associated with preclinical efficacy.

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Prinomastat's mean gel A/B IC_{50} value can be corrected for binding to human plasma in either of two ways, mathematically from its *in vitro* binding to human plasma (analogous to the calculations above) or from the fold-shift in gelatinase A potency determined in the absence/presence of 80% human plasma. By either measure, the PBCed gel A/B IC_{50} value for prinomastat in human plasma (0.22 nM or 0.17 nM) is not too dissimilar from its value determined for mouse plasma (0.26 nM). Applying the 218-fold shift from above to this human PBCed gel A/B IC_{50} value gives prinomastat's "target" efficacious trough concentration of 40-50 nM. Significantly, the trough concentration produced by a 25 mg dose of prinomastat in cancer patients is 47 nM as denoted by the green bar in Figure 1.[3] This represents an "upper limit" of prinomastat exposure since this dose is associated with significant joint toxicity.

The same analysis applied to marimastat produces a similar conclusion. Mouse plasma protein binding was not determined for marimastat, however low binding was observed in rat and monkey plasma (~10%) and a 3-fold shift was observed in its gel A potency in the presence of 80% human plasma. Efficacy in the B16 model using minipump delivery occurred at a marimastat concentration of 167 nM. Based on several clinical trials the trough concentration produced by a 25 mg, bid dose of marimastat is approximately 400 nM.[20, 21] As with prinomastat, this value is not much higher than the trough concentration associated with efficacy in animal models. Interestingly, a recent publication indicates that a 25 mg dose of marimastat given twice daily produces the same survival benefit as gemcitabine in patients with unresectable pancreastic cancer.[11] While this dose produced musculoskeletal effects in nearly half the patients, *most of whom required dosing holidays*, it provides significant evidence of clinical response to MMP inhibition.

As mentioned above, no definitive accounts of preclinical efficacy have been reported for BMS 275291 and we have not characterized this compound in our labs (its structure was revealed as we were winding down our program). The intrinsic potency of BMS 275291 for inhibition of the gelatinases (mean gel A/B IC_{50}: 33 nM) is inferior to the hydroxamate-based compounds and its binding to human plasma was reported to be 46 – 77% (mean = 60%).[15] Without a trough concentration associated with preclinical efficacy BMS 275291 cannot be definitively compared to the other compounds in Figure 1. It is important to recognize, however, that at least one study indicates that trough concentration produced by BMS 275291 in cancer patients peaks at 430 nM (1,800 mg dose); a 2,400 mg dose was associated with a smaller Cmax, AUC(24h) and Cmin.[15] Independent of whether this trend is reproduced in other studies, it does suggest that there may be an upper limit to the exposure of BMS 275291 in humans and that it too may be an inappropriate tool to establish the clinical utility of MMP inhibitors.

ABT-518 is more extensively protein bound than the other compounds in Figure 1 and its affinity differs between mouse and human plasma. It is 94.4% protein bound in mouse plasma and 99.2% protein bound in human plasma which gives rise to a PBCed gel A/B IC_{50} value of 11 nM (mouse) and 80 nM (human). Efficacy in the B16 model was observed at a trough concentration of 260 nM, 23-fold higher than its mouse PBCed gel A/B IC_{50} value. Applying this factor to the human PBCed gel A/B IC_{50} value (80 nM) provides what is arguably an upper limit to the target trough concentration in humans (1,800 nM). Alternatively, using ABT-518's fold shift in gelatinase A potency in the presence of 80% human plasma (53-fold; presumably a more realistic, "functional" correction factor), yields a target trough concentration of 760 nM. These values are in the vicinity of the trough concentrations produced by the 50 mg dose of ABT-518 in cancer patients and would likely be exceeded by slightly higher doses assuming that its exposure continues to be linear with dose. *The inability of competitors' compounds to substantially exceed target trough concentrations could potentially be overcome by ABT-518 if higher doses are absence of adverse effects.*

ABBOTT

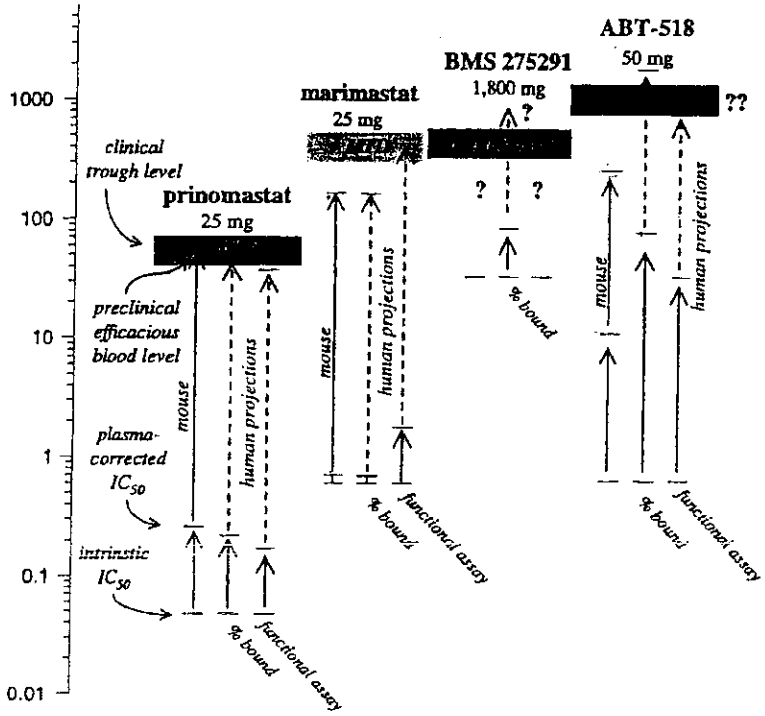
Pharmaceutical Products Division

Steven K. Davidsen, Ph.D.
Senior Project Leader
Cancer Research

Abbott Laboratories
100 Abbott Park Road
D-47J AP10
Abbott Park, Illinois 60064-6100

Tel: 847-937-9113
Fax: 847-935-5165
Email:
steve.k.davidsen@abbott.com

Figure 1. Target versus clinical trough concentrations produced by prinomastat, marimastat, BMS 275291 and ABT-518.



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It is important to mention several caveats associated with the analysis presented above. For example, efficacy projections are based primarily upon data from a single model (B16 murine melanoma). Inhibitors were administered via minipump infusion in order to obtain steady state blood levels that were correlated with efficacy in the model. These steady state levels differ somewhat from the "trough levels" associated with efficacy generally reported in the literature, particularly in the case of prinomastat. Given the requirement for continuous exposure for maximal efficacy, we believe steady state levels provide a more realistic estimate of the required efficacious concentration than do trough levels, especially in the case of prinomastat where there is a large ratio between Cmax and Cmin after oral administration. There are also uncertainties about assessing the impact of plasma protein binding on efficacy as opposed to other factors such as tissue distribution. Given the relatively high affinity these inhibitors have for the target MMPs, the fraction bound in plasma may not accurately reflect the impact on activity. A functional assay of enzyme activity in the presence of plasma would seem to be a better approach and has been sucessfully pursued with human plasma; however, due to the presence of an unknown interfering substance, we have not be able to measure activity in mouse plasma. As mentioned above, we have no preclinical efficacy data for BMS. Rat and monkey plasma binding data were used in place of mouse and human for marimastat.

V. Path Forward

Based on the arguments raised above, the plan for further clinical studies with ABT-518 seems straightforward. First, the unresolved issues surrounding ABT-518's interrupted Phase I study need to be addressed. These include assessing the drug-relatedness of adverse events as well as the plasma concentration of the sulfonic acid metabolite. Second, it would be useful to have additional competitive intelligence on the clinical status of marimastat, prinomastat and BMS 275291, perhaps through Abbott's contacts with clinical oncologists familiar with the MMP inhibitors field. Most importantly, further Phase I studies should be undertaken to determine whether ABT-518 target plasma concentrations can be exceeded in the absence of dose-limiting toxicity. If target plasma concentrations cannot be achieved or if excessive metabolites are produced at these doses, development should be stopped. On the other hand, if ABT-518 crosses these hurdles, trials geared toward the assessment of efficacy should be initiated. It is important that Phase II studies include some measure of MMP activity so that evidence of functional MMP inhibition can be established prior to costly Phase III trials. *In situ* zymography detection of proteolytic activity in resected melanoma biopsies is one potential measure that could be used as a go/no go decision for ABT-518.[22] While conceptually appealing, validation of such a pharmacodynamic assay has not been achieved.

VI. Conclusion

To conclude, we feel that ABT-518 has the potential to be the first MMP inhibitor to demonstrate robust clinical efficacy. The points listed below provide a compelling argument as to why the development of ABT-518 should be continued.

- While the source of the MMPI-induced joint effects has not yet been resolved, the *in vitro* potency and selectivity of ABT-518 differentiates it from marimastat, prinomastat and BMS 275291.
- As a selective MMP inhibitor, ABT-518 exhibits efficacy in cancer animal models equivalent to competitors' compounds.
- Musculoskeletal toxicity limits the dose that can be examined by marimastat and prinomastat in cancer patients. Our analysis suggests that trough concentrations produced by these MMP inhibitors at their MTDs may be insufficient for clinical efficacy.

ABBOTT

Pharmaceutical Products Division

Steven K. Davidsen, Ph.D.
Senior Project Leader
Cancer Research

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Abbott Park, Illinois 60064-6100

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Fax: 847-935-5165
Email:
steve.k.davidsen@abbott.com

- The encouraging human pharmacokinetic data produced by ABT-518, which avoids the large differences in Cmax and Cmin seen with competitors' compounds, suggests that trough concentrations substantially higher than its target levels may be achievable in the absence of limiting toxicity.

Please let me know if you would like to discuss these matters further.

VII. References:

1. Robert Carr Abbott internal email – 7-30-01; 6:20 PM; attached.
2. Robert Carr Abbott internal email – 7-31-01; 3:46 PM; attached.
3. Rugo, H. et al. *Proc. Am. Soc. Clin. Oncol.* **2001**, 20:48a (abstract 187).
4. A-291518 DDC document, page 26.
5. Robert Carr Abbott internal email – 6-8-01; 5:01 PM; attached.
6. A-291518 DDC document, page 27.
7. Rasmussen, H. et al. *Proc. Am. Soc. Clin. Oncol.* **1997**, 16:429a (abstract 1538).
8. Shepherd, F.A. et al. *Proc. Am. Soc. Clin. Oncol.* **2001**, 20:4a (abstract 11).
9. Phuphanich, S. et al. *Proc. Am. Soc. Clin. Oncol.* **2001**, 20:52a (abstract 205).
10. IDdb "marimastat" reference report 407970, News release; May 2, 2001.
11. Bramhall, S.R. et al. *J. Clin. Oncol.* **2001**, 19(15):3447-3455.
12. Ahmann, F.R. et al. *Proc. Am. Soc. Clin. Oncol.* **2001**, 20:174a (abstract 692).
13. Smylie, M. et al. *Proc. Am. Soc. Clin. Oncol.* **2001**, 20:307a (abstract 1226).
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15. Gupta, E. et al. *Proc. Am. Soc. Clin. Oncol.* **2001**, 20:76a (abstract 301).
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18. Hirte, H.W. et al. *Proc. Am. Soc. Clin. Oncol.* **2001**, 20:211a (abstract 843).
19. Klamerus, K. J. et al. *Ann. Mtg Am. Soc. Clin. Pharm. Thera.* **2001**, (poster I-106).
20. Eisenberger, M. et al. *Proc. Am. Soc. Clin. Oncol.* **2000**, 19:336a (abstract 1320).
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22. Ikeda M. et al. *Clin Cancer Res* **2000** 6: 3290-3296.

ASCO 2001 MMPI Update

- Ten MMPI abstracts were presented
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- Patients enrolled to date
  - 25 mg / day 4
  - 50 mg / day 3

  7
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- No musculoskeletal effects reported to date
- Next dose is 100 mg / day

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  Objectives
  - Determine target dose required to achieve target plasma concentration of 1-3 λM
  - Assess safety following chronic administration
- Stop development if Grade 3 or 4 toxicities are attributed to doses at or below target dose
- Stop for joint toxicity
- If target dose is well tolerated, initiate a pharmacodynamic/ proof of principle study with external funds (e.g., NCI-CRADA) and/or outlicense
  - Biopsy multiple melanoma, head and neck cancer, assay for gelatinase A/B activity

INTEROFFICE MEMORANDUM

TO: DAN NORBECK, JOHN LEONARD

FROM: PERRY NISEN

SUBJECT: ABT-518

DATE: 8/14/01

CC: STEVE FESIK, STEVE DAVIDSEN, AZMI NABULSI

Dan asked me to send information that might convince him to revisit the decision regarding ABT-518 development. Attached are the following:

1. Memo from Steve Davidsen summarizing human pharmacokinetics and competitive intelligence
2. Primary pharmacokinetics data from Bob Carr
3. Recent reprints
   - Zymography method to measure inhibition in tissues and a plasma assay (Bremer et al and Duivenvoorden et al)
   - Clinical results of marimistat vs gemcytabine in Pancreatic ca (Bramhall + editorial)- evidence of activity
   - Patients with gel A mutations have oseolytic/arthritic syndrome (Martignetti et al and Vu editorial) –a concern, but probably embryologic

Key points to consider:

- 5 patients were treated: three at 25 mg and two at 50 mg
  - The PK is awesome: half-life 20 hrs, low Cmax/Cmin ratio, low metabolites. In contrast to the competitors', ABT-518 can readily maintain trough concentrations above the target level with once daily dosing (not enough patients treated long enough to determine if there are musculoskeletal effects). We are already at or near the target dose.
    - Adverse events were probably unrelated to drug:
      - One patient who developed venous thrombosis had a history of deep vein thrombosis and was treated with anticoagulants for a year . Anticagulants were discontinued per protocol a month prior to initiating ABT-518

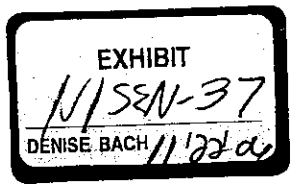
- Another patient who developed renal failure had a prior history of nephrectomy due to tumor invasion and had disease progression in the remaining kidney while on ABT-518

- Clinical trials with competitors' compounds indicates that none of them have the pharmacokinetic properties to enable consistent exposure at the target trough concentration. Furthermore, most of the studies were on patients with advanced, metastatic disease, unlikely to respond to this type of therapy. Nothwithstanding, there is still some evidence for activity (see the marimistat study attached)

Completion of the phase I study would enable us to confirm that we can achieve target trough exposure safely and without musculoskeletal adverse events (~ 10 more patients). A small phase II study could be performed to establish proof of principle: patients with metastatic melanoma can be treated and biopsies assayed by zymography for inhibition of gel A and B as a pharmacodynamic measure. A go/ no go decision can be evidence-based: pharmacodynamics + delayed progression of existing metastases and inhibition of new metastases. This can be accomplished in a 40 patient study. A positive result would restore enthusiasm for the approach and a negative result would be a no go.

I have a meeting scheduled with the NCI to see if they will take over development. I am also having an outlicense package prepared.

37



Gayle A Kirkpatrick /LAKE/GPRD/ABBOTT
09/23/2002 11:20 PM

To: Suzanne Lebold/LAKE/PPRD/ABBOTT@ABBOTT
cc: Ake L Johansson/LAKE/GPRD/ABBOTT@ABBOTT, Thomas J Lyons/LAKE/PPRD/ABBOTT@ABBOTT, William L Mathers/LAKE/GPRD/ABBOTT@ABBOTT
bcc:
Subject: Re: Status of JH compounds/Divestment activities

Suzy,

In response to your email of 9/18 and information needed for an October review wJH, I've polled the SA team and comments are as follows:

ABT-100: no outlicensing activities have been initiated per JHV.

ABT-518: See attached summary from John Fitz Gerald/JHV.

ABT-594: per Kevin and Jim Sullivan, this is not in current development and has NOT been publically communicated. ABT has focused on ABT-202, the back-up cmpd that has a more favorable pdt profile that ABT-594.

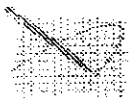
ABT-773: SM has assisted Ake with an outlicensing package

Let me know if any additional information is needed from the SA team

ABT518 Outlicense History.do

Gayle Kirkpatrick
Director, Scientific Assessment & Technology Licensing
Global Licensing and New Business Development
Abbott Laboratories
200 Abbott Park Rd., D50H, AP34-2
Abbott Park, IL 60064-6189

Tel: 847-938-3357
Fax: 847-937-1771
Email: gayle.kirkpatrick@abbott.com
Suzanne Lebold



Suzanne Lebold
09/13/2002 06:55 PM

To: Gayle A Kirkpatrick/LAKE/GPRD/ABBOTT@ABBOTT, Ake L Johansson/LAKE/GPRD/ABBOTT@ABBOTT
cc: William L Mathers/LAKE/GPRD/ABBOTT@ABBOTT, Thomas J Lyons/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Status of JH compounds/Divestment activities

Gayle and Ake:
John Hancock has asked for a status update by 10/15 on the following compounds/outlicensing activities [per the contract, if we drop a compound, activiites to realize the value of the asse]:

- ABT-100 [Gayle, I think that Jane is handling, can you please have her summarize planned activiites]
- ABT-518 [Gayle, do we have a summary of who did evaluate 518- and conclude we have exhausted the supply?] I have some emails- but I don't know that it is complete- lets consolidate, ok?

- ABT-594 [Gayle- can you get an update from Kevin on this- still in 'development' or finally killed?, and do we have plans to outlisc?]
- ABT-773 [Ake- if we could update the process/where we are since the last update that you gave me, which Tom Lyons and I delivered (verbally) to JH on 8/30- thank you.]

Ake has a great summary for 773- timeline of events/who was contacted/status of each/next steps- which I think is appropriate for the others.

Please let me know if you have any queistons or need any additional informtion
JH has a quarterly meeting with Tom Lyons and have asked us to provide this which we are contractually obligated to do. I have Michelle summarizing Article 4 of the agreement to show the rules of the road for each 'bucket' of compounds (and which compounds are treated in which mannet), as they all need to be treated slightly differently in terms of our obligation to 'realize the commercial value of the asset'.

Thank you in advance for your help- if you could please have summaries to me by Oct 11- we can get them to TOm before his meeting with JH-

Suzy

Tom- please confirm that this timing meets your quarterly update needs- thank you.

Suzanne A. Lebold, Ph.D.
Senior Director, Scientific and Strategic Assessment
Global Pharmaceutical Licensing and Business Development
Abbott Laboratories
Phone: (847) 937-1436 Fax: (847) 937-1771
email: suzanne.a.lebold@abbott.com

Abbott Laboratories
Project Overview – ABT 518 - CLOSED

Title: ABT 518 (previously in Ph I)

Deal Type: WW Out-license asset

Background: ABT 518 is a matrix metalloproteinase (MMP) inhibitor program which represents a novel therapeutic class with the potential to alter the way cancer is treated by preventing or modifying disease progression and / or metastases for solid tumors.

Abbott has contacted several companies with little interest to date.

Origination: Due to two other MMP failures in the market (therapeutic window did not occur prior to toxicity (caused severe joint pain) it was decided that this program was too risky. ABT 518 may have promise as the efficacy of has been shown to occur prior to toxicity.

Patent: Approx 2018

Contacts:

Company	Contact	CDA	Status
Chiron	Lauren Miller	??	- No interest
Duke University	Dr. Herb Hurwitz	In process	- No interest on behalf of ABT; Duke wants for free
Paramount Capital	Jeffrey Solash	??	- No interest on behalf of ABT; Paramount interested in option agreement
Salmedix	Alan Rosenthal	Yes	- No interest
Sunessis	Akiko	Yes	- No interest

Time Line / Action Plan:

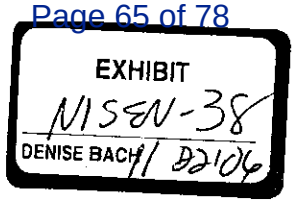
August	ABT valuation of asset
Sept	ABT presentation of confidential data
Sept	ABT Terms sheet to perspective buyers
Oct	ABT selection of final partner / due diligence
Nov / Dec	Contract negotiation / execution

Team Members:
John Fitz Gerald
Jerry Wenker
Jane Hoff-Velk
Perry Nisen / Development
Steve Fesik / Research

Abbott Laboratories
Project Overview – ABT 518 - CLOSED

	Legal / Others
Additional Time:	Medium. (Preparation of slides for presentation, due diligence and contract negotiation).
Deal Terms:	- Upfront, development and regulatory milestones payable to ABT - Royalties on net sales
Other:	- Spending to data and patent being looked into

W
9



Perry D Nisen
05/22/2001 06:27 AM

To: John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT
cc:
cc:
Subject: ABT-518

Attached is a summary of findings on MMPIs from ASCO together with our recommendations for ABT-518. Should I send to Leiden or anyone else after you revise it?

ABT 518 ASCO - Plan May 21, 2001

Diane C Bronson/LAKE/PPRD/ABBOTT
05/28/2001 09:03 PM

To: Diane L D'Amico/LAKE/PPRD/ABBOTT@ABBOTT
cc:
bcc:
Subject: Re: ABT 518 Slides whoops

Diane,

Here are those slides.

I heard that Rob is leaving.

diane
---- Forwarded by Diane C Bronson/LAKE/PPRD/ABBOTT on 05/28/01 09:02 PM ----

Robert Hansen
05/23/01 02:26 PM

To: Diane L D'Amico/LAKE/PPRD/ABBOTT@ABBOTT, Diane C Bronson/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Re: ABT 518 Slides whoops

---- Forwarded by Robert Hansen/LAKE/PPRD/ABBOTT on 05/23/2001 02:26 PM ----

Perry D Nisen
05/22/2001 08:25 AM

To: Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT, Robert Hansen/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Re: ABT 518 Slides whoops

ABT 518 ASCO - Plan May 21, 2001.
---- Forwarded by Perry D Nisen/LAKE/PPRD/ABBOTT on 05/22/01 08:24 AM ----

Perry D Nisen
05/22/01 08:24 AM

To: Robert Hansen/LAKE/PPRD/ABBOTT@ABBOTT, Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Re: ABT 518 Slides

Awesome- I just made some modest changes and will forward to the big dogs
Robert Hansen

Robert Hansen
05/21/01 06:51 PM

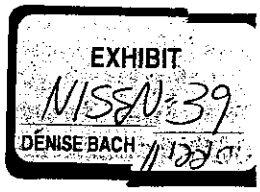
To: Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT
cc: Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT, Steven K Davidsen/LAKE/PPRD/ABBOTT@ABBOTT
Subject: ABT 518 Slides

Perry

Attached please find requested draft slides on MMPI program including ASCO summary, program status, and program recommendation.

Minutes from the Friday ABT-627 DMC Project Review will be available tomorrow morning.

Bob



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  - Biopsy multiple melanoma, head and neck cancer, assay for gelatinase A/B activity

96

Perry D Nisen
06/11/2001 01:25 PM

To: Steven K Davidsen/LAKE/PPRD/ABBOTT@ABBOTT
cc:
cc:
Subject: Re: MMPI data from subject "X" (additional info)

Damn right.
Steven K Davidsen

Steven K Davidsen
06/11/01 03:24 PM

To: Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Re: MMPI data from subject "X" (additional info)

Perry,

This data ain't bad.... damn near target exposure with 25 mg dose. Metabolites are low at 22 days, no apparent induction of metabolism. Independent of whether ABT-518 is pursued further, I think it's safe to say that the decision to take it into clinical studies was not stupid.....

Steve
Perry D Nisen

Perry D Nisen
06/10/01 10:17 PM

To: Steven K Davidsen/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: MMPI data from subject "X" (additional info)

----- Forwarded by Perry D Nisen/LAKE/PPRD/ABBOTT on 06/10/01 10:17 PM -----

Azmi A Nabulsi
06/09/01 10:18 PM

To: Perry Nisen, steven davidsen
cc:
Subject: MMPI data from subject "X" (additional info)

FYI. These are quick calculations that I asked Bob to do once we received the data for on Friday. As you will see, it does not look bad for a 25 mg dose.

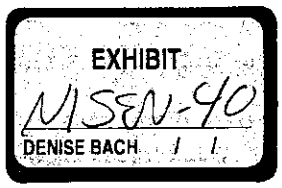
Azmi
----- Forwarded by Azmi A Nabulsi/LAKE/PPRD/ABBOTT on 06/09/01 10:14 PM -----

Robert A Carr
06/08/01 05:01 PM

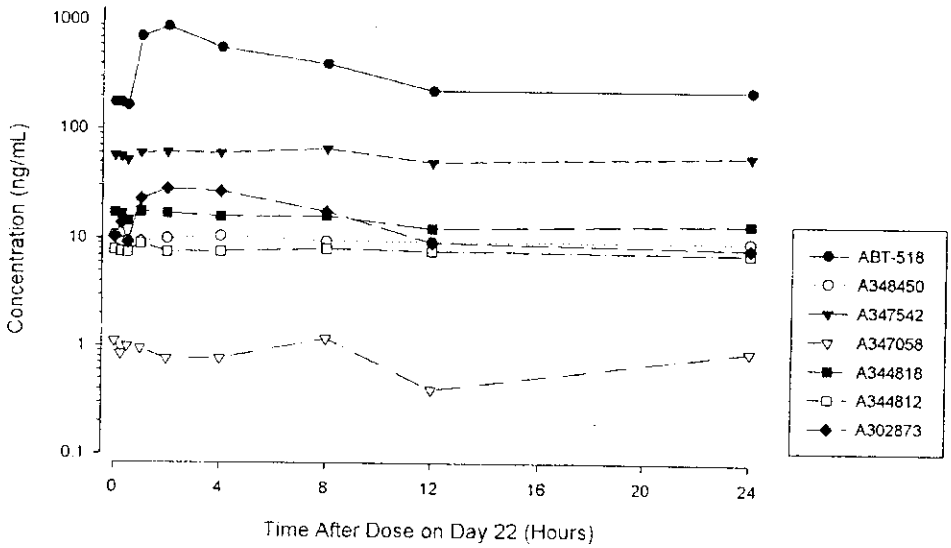
To: Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT
cc: Walid Awni/LAKE/PPRD/ABBOTT@ABBOTT
Subject: MMPI data from subject "X" (additional info)

Azmi,

I believe this subject received 25 mg ABT-518 QD. Following is a plot of parent drug and metabolite concentrations over a 24-hour dosing interval following the dose on Day 22.



Preliminary Concentration Data from Subject "X"



As stated in the transition strategy document (August 2000), if targeted trough concentrations of 100 ng/mL cannot be achieved with oral dosing of ABT-518, or if either an excessive dose (>2 grams) or dosing frequency (more than BID) is required, a No Go recommendation will be made.

The data shown above from one subject indicate that the pharmacokinetic targets for this compound can be met. In this subject, a dose of 25 mg QD achieved trough concentrations of about 200 ng/mL. Steady-state concentrations ranged from about 200 to 900 ng/mL. Metabolite concentrations were very low relative to parent drug. Ratios of AUCs (metabolite to parent) were less than 5%, except for A347542 (16%). Metabolite concentrations appeared to substantially achieve steady state by Day 22.

In mouse efficacy studies, AUC24 values of 2.6 and 22 mcg*h/mL were effective in B16 and HT1080 models, respectively. The AUC24 for Subject "X" was 8.4 mcg*h/mL.

Bob